# Improving the outcomes of anticoagulation

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# ABSTRACT

A number of studies have indicated that adverse events from anticoagulants are significant contributors to health care system expenditure. Adverse events comprise three groups: under-use, over-use and misuse. In Australia, it was estimated in 1992 that adverse events from warfarin cost $100 million in direct hospital costs alone.

Part one of this thesis gives an overview of atrial fibrillation (AF) and the use of antithrombotics. This part provides comprehensive background on the significance of AF and its contribution to stroke and details the extensive evidence of antithrombotic drug efficacy in the prevention of stroke in AF.

Despite overwhelming evidence that antithrombotics are effective in reducing the risk of stroke in AF, they remain under-utilised. Studies conducted internationally and nationally have shown that, in general, less than half of eligible patients receive anticoagulants. Described in part two of this thesis is two studies aimed at improving the use of antithrombotics for stroke prevention in AF.

A nationwide survey of a random sample of general practitioners (GPs), cardiologists and other specialists was undertaken assessing barriers to the use of anticoagulants for stroke prevention in AF. This survey identified a number of key barriers to the use of anticoagulants and identified a number of key interventions to improve the prescribing of anticoagulants. Targeting the identified barriers to the use of anticoagulants, an educational intervention directed at GPs was initiated, aimed at improving the prescribing of antithrombotics in AF. The educational intervention utilised mailed guidelines and the process of academic detailing. The effect of the intervention was analysed using a controlled before and after study design. The educational intervention

significantly improved the use of anticoagulants, but recognised that there is still significant room for more improvement.

Findings of the nationwide survey of doctors identified portable International Normalised Ratio (INR) monitors as a key intervention to improve the prescribing of anticoagulants in AF, and improve the management of existing patients on anticoagulants. Part three of this thesis evaluated the use of portable INR monitors in three practice settings: an outpatient hospital anticoagulant clinic, rural general practices and rural community pharmacies. The portable INR monitors performed well in these three settings. They were found to give accurate and reproducible results when compared to pathology testing and the use of the monitors was well received by GPs, community pharmacists and patients. Findings from these three studies show that the use of portable INR monitors has the potential to significantly reduce health care expenditure associated with anticoagulant therapy, and provides a number of alternative models for anticoagulant management in the community setting.

The final part of the thesis was an intervention aimed at reducing the incidence of bleeding complications amongst patients commenced on warfarin in hospital and discharged to GP care. Patients were randomised to a control or intervention group, where the control group received standard care from their GP and the intervention group received education after discharge and alternate day INR monitoring using a portable INR monitor for four visits after discharge. The intervention significantly reduced the incidence of bleeding complications assessed 90 days after initial discharge, and provided a reproducible model of care for patients commenced on warfarin in hospital and discharged to the community.

The body of work conducted in this thesis provides a number of system solutions aimed at reducing the incidence of anticoagulant-related misadventure and under-use. It is clear that while this thesis provides preliminary evidence that adverse events associated with warfarin can be reduced, more work targeting the use of portable INR monitors in the initiation of warfarin therapy and transfer to the community setting, and education for stroke prevention in AF should continue.

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# PUBLICATIONS

## Peer-reviewed journal publications

Jackson SL, Peterson GM, Vial JH. A community-based educational intervention to improve antithrombotic drug use in atrial fibrillation. Annals of Pharmacotherapy *in press*

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Vial JH, Jackson SL, Peterson GM. Community-based educational intervention improves antithrombotic drug use in atrial fibrillation. Australian Society of Clinical and Experimental Pharmacologists and Toxicologists Annual Meeting, Sydney, November 30-December 3, 2003

Jackson SL, Peterson GM, Vial JH, Jupe D, Marsden K. A randomised controlled trial of point-of-care oral anticoagulant management for patients commenced on warfarin. Society of Hospital Pharmacists of Australia, Federal Conference, Canberra, ACT, November 13-16, 2003.

Jackson SL, Peterson GM, Vial JH. Community-based educational intervention improves antithrombotic drug use in atrial fibrillation. American Heart Association Scientific Sessions, Orlando, Florida, November 9-12, 2003

Jackson SL, Peterson GM, Vial JH, Jupe D, Marsden K. Improving the initial management of anticoagulation in the transition from hospital to general practice care. Royal Australian College of General Practitioners, 46th National Convention & Annual General Meeting, Hobart, Tasmania, October 5-10, 2003.

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Jackson SL, Peterson GM, Vial JH, Jupe D, Marsden K Improving the management of anticoagulation: A randomised controlled trial of point-of-care home follow-up of warfarin therapy. 63rd FIP pharmacy world congress. Sydney, September 4-9 2003.

Jackson SL, Peterson GM, Vial JH, Jupe D, Marsden K Improving the management of anticoagulation: A randomised controlled trial of point-of-care home follow-up of warfarin therapy. Safety and Quality in Action - The Australian Conference on Safety and Quality in Healthcare. Perth, 14-16 July 2003

Jackson SL, Peterson GM, Vial JH, Jupe D, Marsden K. Improving the outcomes of anticoagulation: An evaluation of home follow-up of warfarin therapy. Annual scientific meeting, Royal Australasian College of Physicians. Hobart, May 26-28, 2003.

All publications listed resulted from work described in this thesis

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# ABBREVIATIONS

| | |
|---|---|
| AACP | Australian Association of Consultant Pharmacy |
| ACC | American College of Cardiology |
| ACE | Angiotensin Converting Enzyme |
| ADEs | Adverse Drug Events |
| ADP | Adenosine Phosphate |
| AF | Atrial Fibrillation |
| AFASAK | Atrial Fibrillation, Aspirin, Anticoagulation study |
| AFFIRM | Atrial Fibrillation Follow-up Investigation in Rhythm Management |
| AHA | American Heart Association |
| AMH | Australian Medicines Handbook |
| AMI | Acute Myocardial Infarction |
| APAC | Australian Pharmaceutical Advisory Council |
| ARR | Absolute Risk Reduction |
| BAATAF | Boston Area Anticoagulation Trial |
| CABG | Coronary Artery Bypass Graft |
| CAFA | Canadian Atrial Fibrillation Anticoagulation study |
| CCF | Congestive Cardiac Failure |
| CI | Confidence Interval |
| COX | Cyclooxygenase |
| CT | Computed tomography |
| CYP450 | Cytochrome P450 |
| DDD | Defined Daily Dose |
| DRG | Diagnosis Related Grouping |
| DVT | Deep Vein Thrombosis |

| | |
|---|---|
| ECAA | European Concerted Action on Anticoagulation |
| ECG | Electrocardiograph |
| ESC | European Society of Cardiology |
| ESPRIT | European and Australian Stroke Prevention in Reversible Ischaemia Trial |
| FFP | Fresh Frozen Plasma |
| FHL | Functional Health Literacy |
| GI | Gastrointestinal |
| GP | General Practitioner |
| HM | Home Monitoring |
| INR | International Normalised Ratio |
| IRP | International Reference Preparation |
| ISI | International Sensitivity Index |
| IV | Intravenous |
| J | Joules |
| LA | Left Atrium |
| LAA | Left Atrial Appendage |
| LMWH | Low-molecular weight heparin |
| LV | Left Ventricular |
| NATA | National Association of Testing Authorities |
| NNT | Number Needed to Treat |
| NPS | National Prescribing Service |
| NSAIDs | Non-steroidal Anti-Inflammatory Drugs |
| NVAF | Non Valvular Atrial Fibrillation |
| PAF | Paroxysmal Atrial Fibrillation |

| | |
|---|---|
| PATCH | Patients Acute Treatment and Care in the Home |
| PBS | Pharmaceutical Benefits Scheme |
| PE | Pulmonary Embolus |
| PIAF | Pharmacological Intervention in Atrial Fibrillation trial |
| PT | Prothrombin Time |
| QUM | Quality Use of Medicines |
| RACE | Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation |
| RCT | Randomised Controlled Trial |
| RPBS | Repatriation Pharmaceutical Benefits Scheme |
| RRR | Relative Risk Reduction |
| SC | Subcutaneous |
| SPAF | Stroke Prevention in Atrial Fibrillation |
| SPINAF | Stroke Prevention in Nonvalvular Atrial Fibrillation |
| SPORTIF | Stroke Prevention using Oral Thrombin Inhibitor in Atrial Fibrillation |
| STAF | The Strategies of Treatment of Atrial Fibrillation study |
| TIA | Transient Ischaemic Attack |
| TOE | Transoesophageal Echocardiography |
| $TXA_2$ | Thromboxane $A_2$ |
| UC | Usual Care |
| UDRH | University Department of Rural Health |
| VTE | Venous Thromboembolism |
| WHO | World Health Organisation |

# PART ONE: OVERVIEW OF ATRIAL FIBRILLATION AND ANTITHROMBOTIC THERAPY

## CHAPTER ONE: ATRIAL FIBRILLATION

### 1.1 Definition

Atrial Fibrillation (AF) is a supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with subsequent deterioration of atrial mechanical function. AF is characterised by the replacement of consistent P waves that vary in size, shape and timing with "irregularly irregular" ventricular contractions Figure 1. [1, 2] Normally, heart rate is correlated with the body's physiological needs by the sinoatrial node, which maintains a rate of about 60 beats per minute at rest. During AF, atrial cells can fire at rates of 400-600 times per minute. [3] If each atrial impulse were conducted to the ventricles, the extremely rapid ventricular rate would lead to ineffective cardiac contraction and death. [3] The ventricular rate during AF is in the region of 150 times per minute in the absence of drug therapy. [3] AF may occur in isolation or in association with other arrythmias, most commonly atrial flutter or atrial tachycardia. [1] Atrial flutter may degenerate into AF. AF may also initiate atrial flutter or the ECG pattern may alternate between atrial flutter and AF. [1]

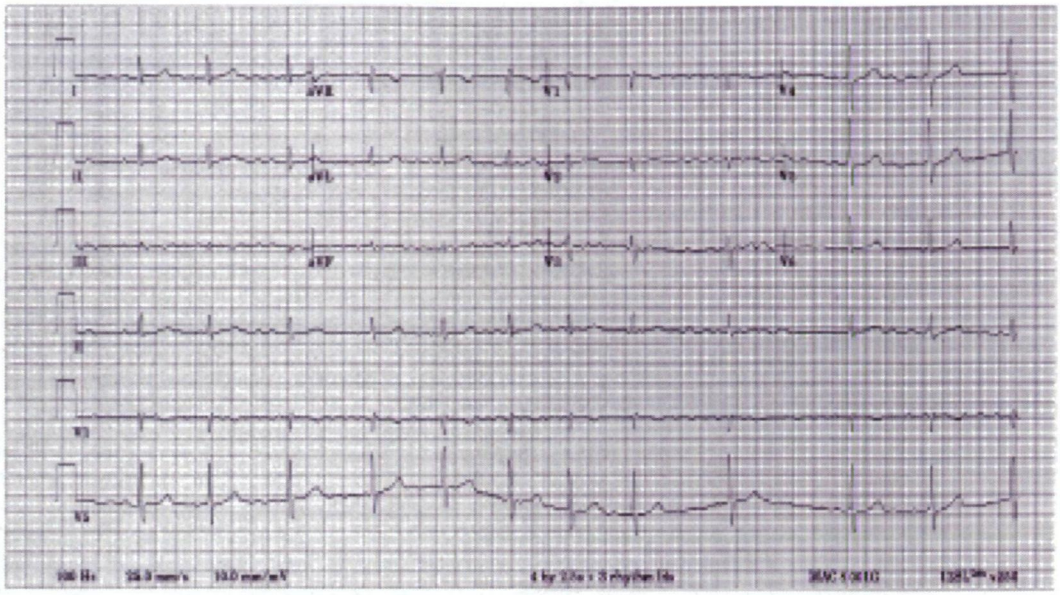


**Figure 1 Standard 12-lead electrocardiograph displaying AF.**
Reproduced from ACC/AHA/ESC guidelines for the management of patients with AF. [1]

## 1.2 Classification

AF can have very diverse clinical presentations. It can occur in the absence or presence of detectable heart disease or related symptoms. [1] An episode of AF may be self-limited or require medical intervention for termination. The pattern of AF may be defined in terms of the number of episodes, duration, frequency, mode of onset, possible triggers and response to therapy. [1] However, these features may be impossible to identify when AF is first encountered in an individual patient.

A number of types or classifications of AF have been used to describe the pattern of AF, however there is no universal consensus on the nomenclature or classification of AF. Some proposed types have included acute, chronic, paroxysmal (PAF), intermittent, constant, persistent and permanent. A simple and clinically relevant classification has been proposed by the American College of Cardiology/American Heart Association/ European Society of Cardiology (ACC/AHA/ESC) practice guidelines for the management of AF (Figure 2). [1] At

presentation with a first detected episode of AF, it needs to be assessed whether it is symptomatic or self-limited, whilst recognising there may be uncertainty about the duration of the episode and about previous undetected episodes. [1] Recent guidelines have proposed that classification be redefined according to treatment. The "three P's" of the new classification system are "paroxysmal," "persistent," and "permanent" (Figure 2). [1]

When a patient has had 2 or more episodes, AF is considered recurrent. If the arrhythmia terminates spontaneously, recurrent AF is considered paroxysmal, if the arrhythmia is sustained it is designated persistent. In the case of persistent AF, it may require reversion by pharmacological or electrical mechanisms. [1] The terms chronic AF and Permanent AF are sometimes used interchangeably and are when AF is present on a permanet basis.

About a quarter of diagnosed cases of AF are paroxysmal. [4, 5] Patients with PAF tend to be younger and have less comorbid illness than those with persistent AF. Limited data suggest that roughly 20% of patients with PAF will progress to sustained AF over a 4-year period. [6] The category PAF covers a wide spectrum of rhythm abnormalities, varying by frequency and length of AF episodes. For example, in a recent large trial, 12% of patients with PAF had more than 1 episode daily, while another 25% reported only 1 episode every 6 months. [7]

AF can be acute (episodes last less than 30 seconds) and occur in relation to a reversible cause. Common causes of acute AF are: acute myocardial infarction, (AMI) cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism (PE), and infections. In these circumstances, AF is not the primary problem and treatment of the underlying disorder with management of the AF usually results in termination of the arrhythmia without recurrence. [1]

"Lone AF" generally applies to young individuals (under 60 years of age) without clinical or echocardiographic evidence of cardiac disease. [1] In general, the frequency of lone AF is less than 10%. [8] These individuals have a favourable prognosis with respect to thromboembolism and mortality. However, as time goes by, cardiac abnormalities can develop such as enlargement of the left atrium (LA). The term "non-valvular AF" (NVAF) is given to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease or a prosthetic valve. [1]

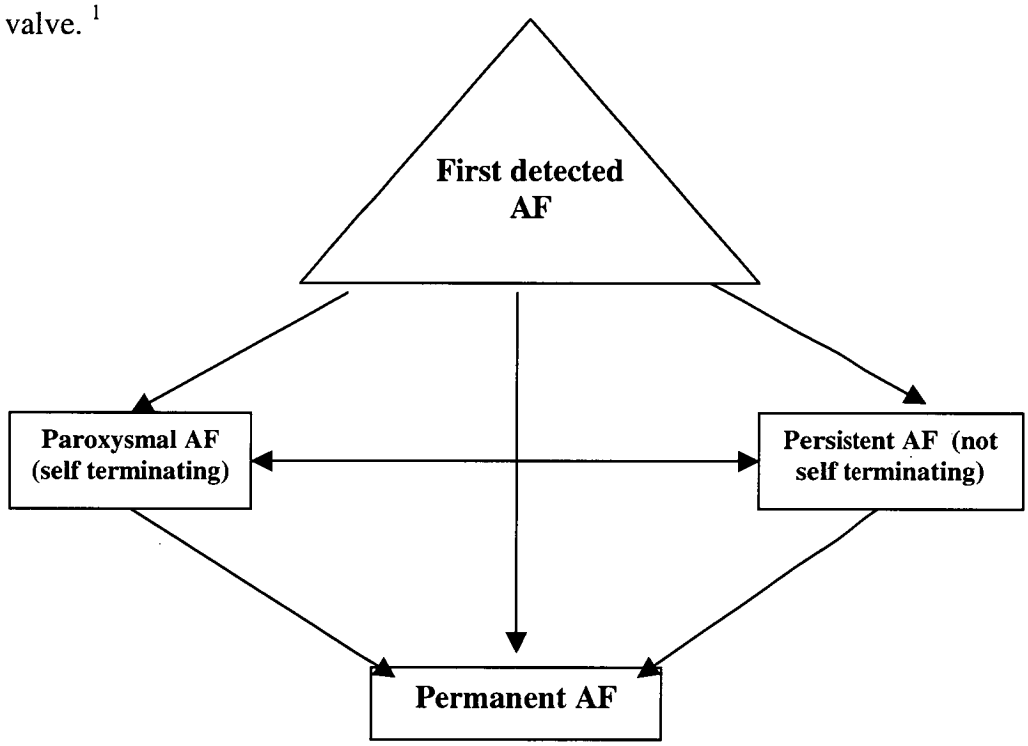



**Figure 2 Classification system for different types of AF.**
Reproduced from ACC/AHA/ESC guidelines for the management of patients with AF. [1]

## 1.3 Epidemiology and risk factors

AF is the most common rhythm abnormality, and much of our knowledge comes from the Framingham Heart study. [9] The prevalence of AF is estimated to be 0.4%-1% of the general population and increases with age. [1, 5] The prevalence of

AF is less than 1% in those under 60 years of age and reaches 10% in those over 80 years (Figure 3). [8, 10-12] AF is prevalent in patients with congestive cardiac failure (CCF) and valvular disease and the incidence increases with the severity of these conditions. [1] AF commonly complicates cardiac surgery and AMI. Multivariate analysis has identified increasing age, CCF, smoking, diabetes, hypertension, male gender, left ventricular (LV) hypertrophy, AMI and valvular heart disease as risk factors for the development of AF. [9] AF is an independent risk factor for death, with a relative risk factor for death of 1.5 for men and 1.9 for women after adjustment for known risk factors. [13] As the baby boom generation reaches its 70s and 80s, the prevalence of AF will increase markedly. AF is often asymptomatic, therefore, it may occur even more frequently than estimates suggest.[14]

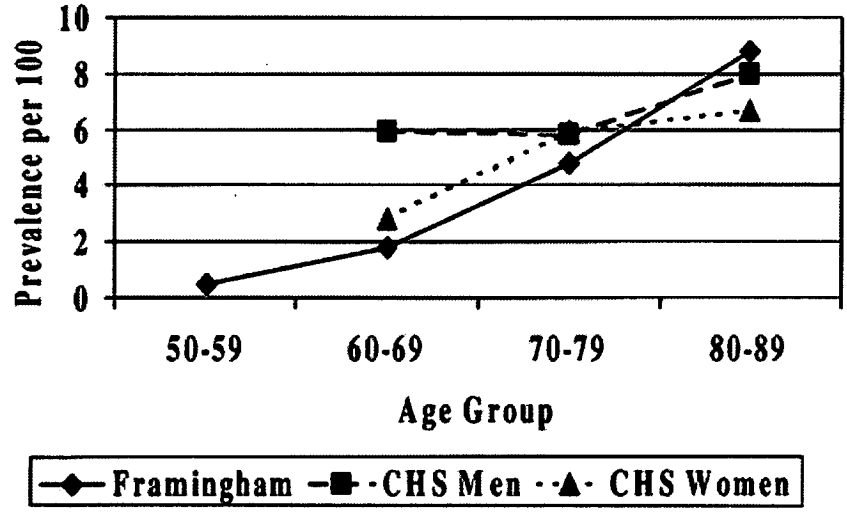



**Figure 3 Prevalence of AF in 2 American epidemiological studies. The Framingham Heart Study and the Cardiovascular Health Study (CHS).** Reproduced from Furberg et al. [8]

## 1.4 Mechanisms of AF

The traditional view of AF mechanisms is, that the arrhythmia results from multiple re-entrant wavelets that move randomly throughout the atria, colliding, being extinguished, and arising again. [2, 15] Re-entry is promoted by decreased atrial refractory periods, slowed conduction and an increased mass of cardiac tissue. Recently it has been shown that atrial tachyarrhythmias, including AF, alter atrial electrical properties promoting multiple-circuit re-entrant AF. [2] A second distinct mechanism causing AF has recently been recognised, a rapidly firing focus (or foci), usually located in or near the pulmonary vein. [3, 15, 16] Catheter ablation of AF is a useful approach for patients with symptomatic AF recurrences, it reduces the frequency of recurrent AF in the majority of patients, however, the risk of recurrent AF is 30% to 50% over the first year. [1]

Sustained AF causes important reductions in cellular contractility, resulting in tachycardia-induced atrial cardiomyopathy that may be responsible for delayed thromboembolic events as contractility recovers after cardioversion. [2] Shortening of the atrial refractory period is a fundamental change that helps to perpetuate the arrhythmia, by allowing more wavelets in the atrial mass. Paroxysmal and persistent AF are associated with shortening of the atrial refractory period, but this change can become more permanent in long-term AF. This gives rise to the adage that "AF begets AF" the notion that AF tends to perpetuate itself.

Individuals with recurrent AF can develop increasing problems over time and many progress to permanent AF. [15] The ability to cardiovert to sustained sinus rhythm is greatly reduced in patients who have been in persistent AF for longer than 12 months. [15] Atrial hypertrophy and dilatation may be either a cause

of or a consequence of persistent AF, because progressive atrial enlargement has been demonstrated in patients with AF. [17] Renin-angiotensin activation appears to play an important role in CCF-related atrial remodeling, which can be attenuated by treatment with an angiotensin converting enzyme (ACE) inhibitor. [2] AF may result from increased vagal tone that leads to episodes during sleep, after meals, from alcohol and or caffeine. [1]

## 1.5 Acute AF

Common causes of acute AF are: AMI, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, PE, and infections. Although AF may occur after noncardiac surgery, the incidence of atrial arrhythmias after open-heart surgery is between 20 and 50%. [18, 19] Postoperative AF usually occurs within five days of cardiac surgery, with a peak incidence on day 2. A number of studies have shown an increased risk of stroke in coronary artery bypass graft (CABG) patients after the procedure, so anticoagulation is appropriate when AF persists for more than 48 hours. [20, 21]

## 1.6 Haemodynamic consequences

AF is associated with the loss of the atrial contribution to ventricular filling [15] and can result in a decrease in ventricular stroke volume of up to 20 percent. [15] Three factors can contribute to deterioration in haemodynamic function: loss of synchronous atrial activity, irregularity of ventricular response, and an inappropriately rapid heart rate. [1] A marked decrease in cardiac output may occur

with the loss of atrial contraction, especially in patients with impaired ventricular filling, hypertension, mitral stenosis and cardiomyopathy. [1] A persistently elevated ventricular rate during AF can produce tachycardia-induced cardiomyopathy. [1]

## 1.7 Clinical manifestations

AF may be symptomatic or asymptomatic, [2] even in the same patient. [1] In fact, asymptomatic episodes occur more frequently than symptomatic ones. [14] The arrhythmia may present for the first time with an embolic complication or exacerbation of CCF, but most patients with AF complain of palpitations, chest pain, dyspnoea, fatigue, lightheadedness, or syncope, [1] however, Fatigue and other non-specific symptoms are the most common. [22] The cognitive function of elderly patients with persistent AF is lower compared to age-matched controls in sinus rhythm. [23] AF may be associated with a fast ventricular response, leading to tachycardia-induced cardiomyopathy, especially in patients who are unaware of the arrhythmia. [1] Symptoms vary with the ventricular rate, underlying functional status, duration of AF, and individual patient perceptions. [1] Data suggests that the quality of life for patients during AF is significantly impaired as compared to the quality of life after sinus rhythm is restored. [15]

## 1.8 Examination and investigations

The initial evaluation of a patient with suspected or proven AF includes elucidating the pattern of the arrhythmia as paroxysmal or persistent, determining

its cause and defining associated cardiac factors. [1] The evaluation of a patient with AF can be implemented in an outpatient encounter, but delays can occur when the rhythm have not been specifically or successfully documented. The diagnosis of AF requires electrocardiograph (ECG) documentation, which may be facilitated by review of emergency department records, Holter monitoring, or transtelephonic or telemetric recordings. If episodes are frequent, a 24-hour Holter monitor can be used. If episodes are infrequent, then an event recorder may be used [1] (not currently used in Australia).

Transoesophageal echocardiography (TOE) places high-frequency ultrasound transducers in close proximity to the heart to provide high-quality images of cardiac structure and function. [24, 25] It is the most sensitive and specific technique to detect sources and potential mechanisms for cardiac embolism.

## 1.9 Thromboembolism

The rapid and irregular atrial activity causes a loss of atrial contraction, in which the atria only quiver, leading to stasis of blood in the atria. [3] This promotes clot formation and the occurrence of thromboemboli. [3] The left atrial appendage (LAA) is an elongated cul-de-sac lined with endothelium, a remnant of the embryonic atrium and a unique substrate for stroke. [26] The contractility of the appendage is reduced in AF, but the degree varies widely and is an important determinant of stasis and thrombus formation. Stasis is fundamental to the formation of LAA thrombi in AF. Formation of a thrombus in the LAA begins with Virchow's conditions of: stasis, endothelial dysfunction, and a hypercoagulable state. [1] The LAA is the origin of at least 90% of all left atrial

clots [27] and the resulting systemic emboli cause approximately 25% of all strokes.[27]

TOE provides a sensitive and specific method to detect thrombotic material (Figure 4). [1] Conventional management is based on the presumption that thrombus formation requires continuation of AF for approximately 48 hours, but thrombi have been identified by TOE within shorter intervals. [28, 29] Endothelial dysfunction has been difficult to demonstrate as a distinct mechanism contributing to thrombus formation, although systemic and atrial tissue levels of von Willebrand factor (a marker of endothelial dysfunction) are elevated in some patients. [1] AF has been associated with elevated levels of biochemical markers of coagulation and platelet activation (fibrinogen and fibrin D-dimer levels) that may reflect a systemic hypercoagulable state. [30] The levels of some of these markers fall to normal during anticoagulation therapy [31] and some markers increase immediately after conversion to sinus rhythm and then normalise. [32] Thromboemboli tend to propagate, particularly to the brain (approximately 25% of blood from the heart supplies the brain) but also to other organs (including the kidneys, mesenteric circulation and the heart itself), potentially leading to infarction. [3]

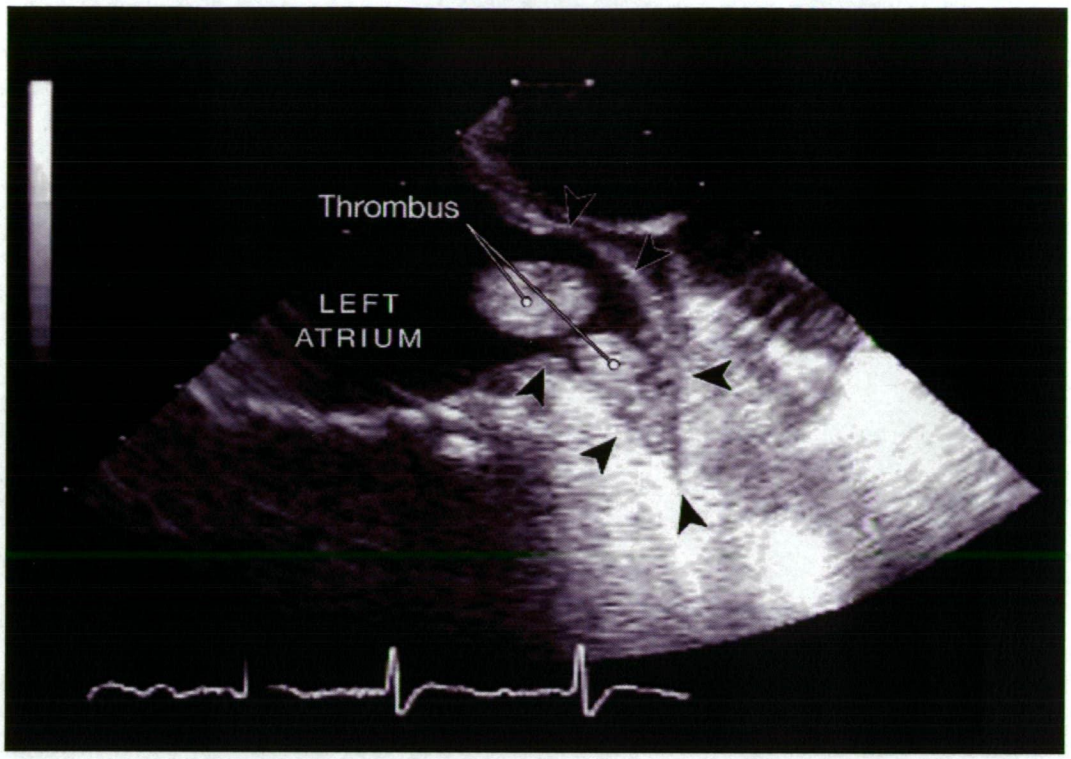



**Figure 4 Transesophageal echocardiographic image of a thrombus in the left atrial appendage in a patient with AF.**
Reproduced from ACC/AHA/ESC guidelines for the management of patients with AF. [1]

Recently, high plasma homocysteine has shown to be an independent risk factor for LA thrombus formation in patients with stroke caused by AF. [33] High homocysteine fulfills 2 criteria of Virchow's triad by its endothelial toxic effect and prothrombotic properties. [33] In conditions associated with abnormal blood flow such as stasis, high levels of homocysteine enhance thrombus formation.

## 1.10 Stroke

Stroke is defined by the World Health Organisation (WHO) as the clinical syndrome of rapid onset of focal (or global, as in subarachnoid haemorrhage) cerebral deficit, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one. [34]

The most feared complication of AF is stroke. AF is associated with a five-fold increase in the risk of stroke compared to age-matched controls. Most patients with atrial fibrillation never experience a stroke. [35] The stroke rate varies more than 20-fold, from 0.5% for young patients with lone AF [36] to 12% per year for patients with AF who have had a previous stroke. [37-39] Embolism even in patients with chronic, sustained AF can be intermittent, separated by days or years, suggesting that the formation of LAA thrombi occurs intermittently.[26] Embolism of LAA thrombi accounts for most strokes in AF patients, particularly the larger, more disabling strokes. [26] About two-thirds of strokes in AF patients are due to atrial thrombi. This varies according to the distribution of additional risk factors and antithrombotic therapy. [26]

The diagnosis of stroke (versus no stroke) is made, reasonably accurately on clinical grounds alone, by specialists, but in general medical and emergency-department settings up to 15% of patients with suspected stroke turn out to have another diagnosis. [40] Infarction cannot be reliably distinguished from haemorrhage without brain imaging. Whichever imaging method is used, the radiologist needs to know the time and date of stroke onset to interpret the images properly. Computed tomography (CT) is the most reliable method of demonstrating acute haemorrhage within the first week after stroke onset. Small haemorrhages progressively lose their characteristic white (hyperdense)

appearance and can easily be mistaken for infarcts, therefore, if patients delay seeking medical attention, perhaps because the stroke symptoms were mild, or if their doctors delay scanning, imaging might not be done until 2 weeks or longer after the stroke; an infarct could then be misdiagnosed on CT, and inappropriate management could follow. [41, 42]

CT may or may not show a definite infarct, but a normal scan does not necessarily mean that the patient have not had a stroke. CT is quick and can be done in almost all patients, however ill. Its value in excluding haemorrhages and tumours more than outweighs any deficiency in positively identifying infarcts. About 50% of infarcts never become visible on CT; the proportion is higher in patients with milder strokes (lacunar and small cortical or brainstem infarcts) and lower in patients with severe strokes (medium to large cortical or cerebellar infarcts). The proportion visible also depends on the timing of scanning. Within the first few hours, few infarcts can be seen, [43] but they become visible over the first 1-7 days as dark hypodense wedge-shaped areas (or round if lacunar), with mass effect.

## 1.11 Risk factors for stroke

The rate of stroke in patients with AF is related to the presence of concomitant cardiovascular disease. [36, 44, 45] There is a strong association between hypertension and stroke, probably mediated primarily by embolism originating in the LAA, [46] due to reduced LAA flow velocity. [47, 48] Hypertension also increases the risk of noncardioembolic strokes in AF. [46, 49] Whether sustained control of hypertension lowers the risk for cardioembolic stroke remains unclear. In addition to

hypertension, prior thromboembolism, CCF and diabetes have emerged as independent risk factors for stroke. [36, 37, 45] A list of predictive risk factors for stroke is displayed in Table 1. Table 2 displays relative risks of some risk factors for stroke in patients with AF compared to control patients without AF.

| |
|---|
| **Consistent independent predictors** |
| Advancing age |
| Hypertension |
| Prior stroke or transient ischaemic attack (TIA) |
| Left ventricular dysfunction (clinical CCF or systolic dysfunction on echocardiography |
| **Possible independent predictors** |
| Diabetes mellitus |
| Systolic blood pressure > 160 mm Hg |
| Women over age 75 |
| Post menopausal hormone replacement therapy |
| Regular alcohol use (>14 drinks/2weeks) (decreased risk) |
| Coronary artery disease |
| Postoperative status |
| Mitral regurgitation (decreased risk) |
| **On TOE:** appendage thrombi, spontaneous dense echocontrast, reduced appendage flow velocity |
| **Not independently predictive** |
| Left atrial diameter |
| Intermittency (i.e., paroxysmal) |

**Table 1 Predictors of ischaemic stroke in AF**
Adapted from Hart and Halperin. [26]

| Risk factors (control groups) | Relative risk |
|---|---|
| Previous stroke | 2.5 |
| History of hypertension | 1.6 |
| CCF | 1.4 |
| Advanced age (continuous, per decade) | 1.4 |
| Diabetes mellitus | 1.7 |
| Coronary artery disease | 1.5 |

**Table 2 Risk factors for ischaemic stroke and systemic embolism in AF.**
Adapted from Laupacis et al. [36]

Nearly half of all strokes occur in patients over 75 years of age and AF is the most frequent cause of disabling stroke in elderly women. [10] The effect of advancing age in increasing stroke risk is multifactorial. In patients with AF, aging is associated with LA enlargement and reduced LAA flow velocity all of which predispose to LA thrombus formation. [17, 47] Age is also a risk factor for atherosclerosis and is associated with stroke independently of AF. [50] In the Stroke Prevention in Atrial Fibrillation (SPAF) studies, age was a more potent risk factor when combined with other risk factors such as hypertension or female gender, [37] placing women over the age of 75 years with AF at particular risk for cardioembolic strokes. [51] LV dysfunction, as indicated by a history of CCF or transthoracic echocardiographic measurements, predicts ischaemic stroke in AF patients who receive no antithrombotic therapy. [44, 45, 52] In the SPAF study, the annual rate of stroke was similar for patients with recurrent or permanent AF. [53]

## 1.12 Risk stratification criteria

Estimating the risk of stroke for individual AF patients is a crucial factor in the decision to use antithrombotic therapy for individual patients with AF, [35] and accurate prediction of stroke risk has become an important clinical issue. A number of clinical schema have been proposed in the literature to categorise an individual risk of stroke, in view of making the choice of antithrombotic therapy easier. Displayed in Table 3 are five clinical schemes to stratify the risk of ischaemic stroke in AF patients based on analysis of prospectively monitored cohorts of participants and expert opinions. [54, 55] Each of the schema is predictive

of stroke, but the small differences between them can be sometimes very important for individual patient management.

| Risk | | | |
|---|---|---|---|
| **Study** | **High** | **Intermediate** | **Low** |
| Atrial Fibrillation Investigators [56] | ▪ High to intermediate risk: Age > 65 years. History of hypertension or diabetes | | ▪ Age < 65 years.<br>▪ No high risk features |
| American College of Chest Physicians Consensus [57] | ▪ Age > 75 years<br>▪ History of hypertension, left ventricular dysfunction or > 1 moderate risk factor | ▪ Age 65-75 years<br>▪ Diabetes or coronary artery disease | ▪ Age < 65 years<br>▪ No risk factors |
| Stroke Prevention in Atrial Fibrillation study [58] | ▪ Women aged > 75 years<br>▪ Systolic blood pressure > 160 mm Hg or left ventricular dysfunction | ▪ History of hypertension<br>▪ No high risk features | ▪ No high risk features<br>▪ No history of hypertension |
| Lip (United Kingdom) [59] | ▪ Patients aged > 75 years and with diabetes or hypertension<br>▪ Patients with clinical evidence of CCF, thyroid disease, and impaired left ventricular function on echocardiography | ▪ Patients aged < 65 years with clinical risk factors: diabetes, hypertension, peripheral arterial disease, ischaemic heart disease<br>▪ Patients aged > 65 not in high risk group | ▪ Patients aged < 65 years with no risk factors |
| Hankey (Australia) [60] | ▪ Age > 65 years and hypertension or diabetes<br>▪ Previous TIA or stroke<br>▪ Recent myocardial infarction<br>▪ CCF or impaired left ventricular dysfunction on echocardiography<br>▪ Thyroid disease or left atrial thrombus | ▪ Age < 65 years and hypertension or diabetes<br>▪ Age > 65 years and not in high risk group | ▪ Age < 65 years and no hypertension, diabetes, TIA, stroke or other clinical risk factors |

**Table 3 Published risk stratification schema prevention of stroke in AF.**

## 1.13 Treatment of AF

### 1.13.1 Rate control

The major issues in management of patients with AF are related to the arrhythmia itself and to the prevention of thromboembolism. In patients with persistent AF, there are 2 ways to manage the arrhythmia: to restore and maintain sinus rhythm or to allow AF to continue and ensure that the ventricular rate is controlled (Table 4). [1] The criteria for rate control vary with patient age. The rate is generally considered controlled when the ventricular rate ranges between 60 and 80 beats per minute at rest and between 90 and 115 beats per minute during moderate exercise. [1]

| Drug | Usual maintenance dose (oral) for elderly | Major side effects |
|---|---|---|
| Digoxin | 62.5-125μg once daily (doses may be higher in some individuals) | Digitalis toxicity, heart block, bradycardia |
| Diltiazem | 180-360mg once daily | Hypotension, heart block, heart failure |
| Verapamil | 160-240mg daily | Hypotension, heart block, heart failure, digoxin interactions, constipation |
| β-Blockers | | Hypotension, heart block, bradycardia, asthma, heart failure, fatigue |
| Atenolol | 25-50mg once daily | |
| Metoprolol | 25-50mg once daily | |
| Carvedilol | Titrated to heart failure response (may be particularly useful for patients with AF and CCF) | |
| Amiodarone | 200-400mg three times daily for 1 week, then 200-400mg twice daily for 1 week, then maintenance dose of 200-400mg daily | Pulmonary toxicity, skin discolouration, hypo- and hyperthyroidism, corneal deposits, optic neuropathy, warfarin interactions and proarrhythmia |

**Table 4 Oral agents commonly used for rate and rhythm control in AF**

### 1.13.2 Rhythm control

Reasons for restoration and maintenance of sinus rhythm in patients with AF include relief of symptoms, prevention of embolism, and avoidance of cardiomyopathy. [1] The decision to convert AF (as opposed to controlling the rate and allowing AF to continue) is commonly intended to alleviate all these problems. Conversion to and maintenance of sinus rhythm offers the theoretical advantages of reducing the risk of thromboembolism, but has been questioned recently. [61]

### 1.13.3 Rationale for cardioversion

Cardioversion is often performed electively to restore sinus rhythm in patients with persistent AF. The need for cardioversion may be immediate when the arrhythmia is the main factor responsible for acute CCF, hypotension and angina. Cardioversion carries a risk of thromboembolism unless anticoagulation prophylaxis is given before the procedure, and this risk appears greatest when the arrhythmia has been present for more than 48 hours. [1]

### 1.13.4 Pharmacological cardioversion

Whether AF is paroxysmal or persistent, AF is a chronic disorder and recurrence is likely at some point in most patients. [62, 63] Pharmacological cardioversion appears to be most effective when initiated within 7 days after the onset of AF (Table 4). [1] The reversion to sinus rhythm is much less effective in patients with persistent AF.

### 1.13.5 Direct current cardioversion

Direct current cardioversion involves delivery of an electrical shock synchronised with the intrinsic activity of the heart. Successful cardioversion of AF depends on the nature of the underlying heart disease and the intensity of the shock delivered to the atrial myocardium. The initial energy delivered may be as low as 50 joules (J) for conversion of atrial flutter, but higher energies are needed for AF conversion, starting with at least 200 J. The energy output is increased successively in increments of 100 J until a maximum of 400 J is reached. The success of cardioversion is related to: the size and composition of the electrode paddles, the contact medium between the electrodes and skin, the distance between the paddles, body size, phase of the respiratory cycle, number of shocks delivered and interval between shocks. [1] Rates of successful cardioversion vary from 70% to 90%, with diminishing success rates if the arrhythmia has been present for longer than one year. [64] Multivariate analysis has revealed short duration of AF and younger age as independent predictors of success. In contrast, LA enlargement, underlying heart disease and cardiomegaly predicted failure. [64]

The rate of relapse after cardioversion is high unless concomitant antiarrhythmic drug treatment is given.

### 1.13.6 Cardioversion to sinus rhythm and risk of thromboembolism

A higher risk of stroke had been identified in patients undergoing cardioversion of AF, and this could be reduced with pre-treatment with anticoagulation for 3 to 4 weeks before and after cardioversion. [65] Nowadays, it is common practice to administer oral anticoagulants to patients with AF of more than 48 hours duration when they are prepared for cardioversion. Cardioversion of AF to sinus rhythm results in transient mechanical dysfunction of the LA and LAA [66] known as "atrial stunning," which can occur after spontaneous, pharmacological [67, 68] or electrical conversion of AF. [68] Recovery of mechanical function may be delayed for several weeks, depending on the duration of AF before cardioversion. [69, 70] This could explain why some patients with no demonstrable LA thrombus on TOE before cardioversion subsequently experience thromboembolic events. [71] Presumably, a thrombus forms during the period of atrial stunning and is expelled after the return of mechanical function, which may explain the cluster of thromboembolic events that occur in the first 10 days after cardioversion. [72]

# CHAPTER TWO: ANTITHROMBOTICS

## 2.1 Warfarin

### 2.1.1 Mechanism of action

Warfarin is the most widely used anticoagulant in the western world. It exerts its anticoagulant effect by interfering with the interconversion of vitamin K quinol and its 2,3 epoxide (vitamin K epoxide) (Figure 5). Vitamin K (phylloquinine) is a co-factor needed for the carboxylation of glutamate residues to γ-carboxyglutamates of vitamin K-dependent proteins. [73] These proteins, which include the coagulation factors II, VII, IX & X, require γ-carboxylation by vitamin K for biological activity. By inhibiting the vitamin K conversion cycle, warfarin causes hepatic production of partially decarboxylated proteins with reduced coagulant activity, which in turn exerts an anticoagulant effect (Figure 6). [73] Vitamin K antagonists also inhibit the carboxylation of the regulatory anticoagulants protein C and protein S.

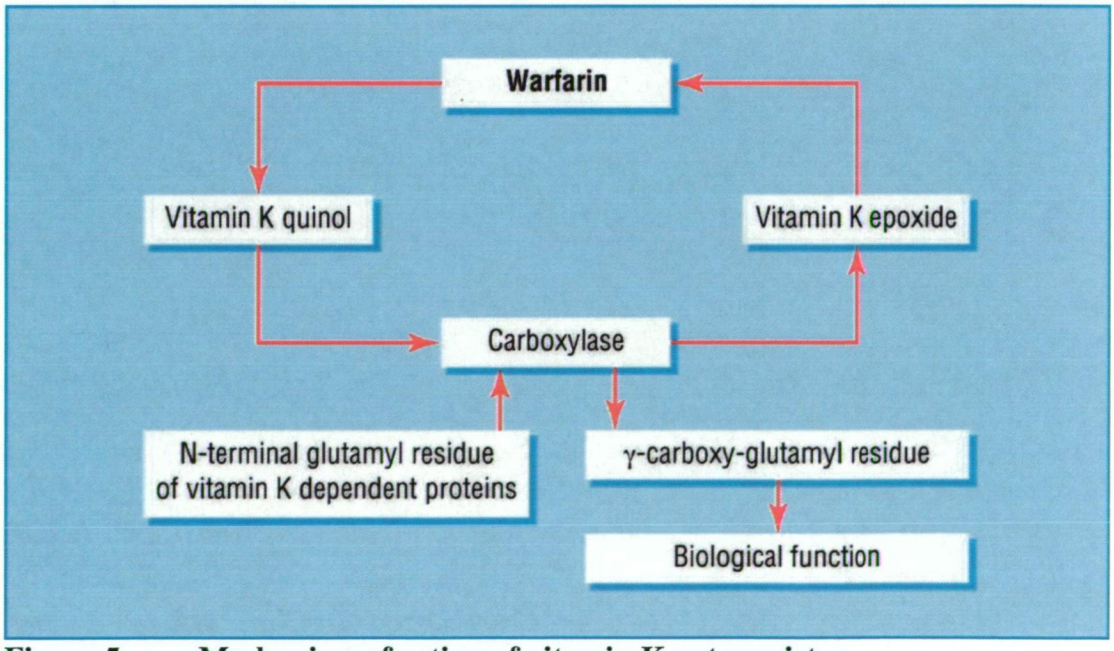



**Figure 5 Mechanism of action of vitamin K antagonists.**
Reproduced from Blann et al. [74]

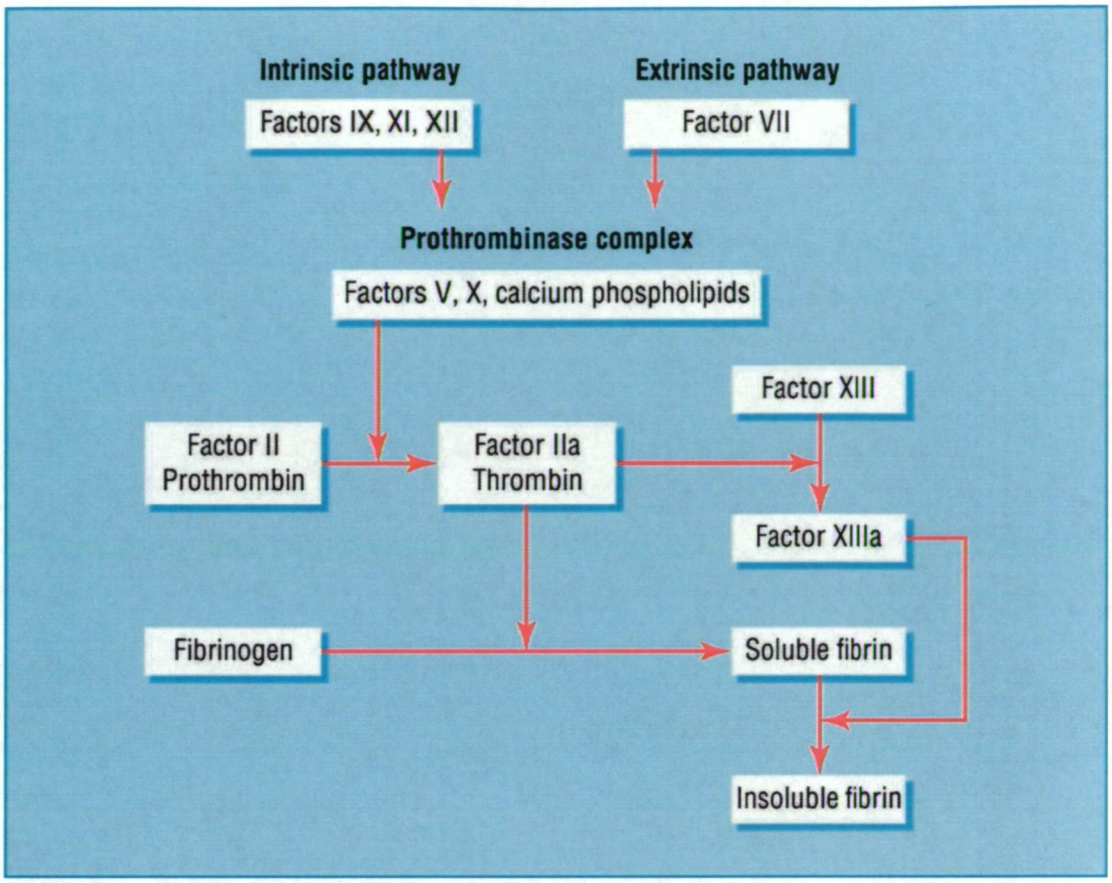



**Figure 6 Description of the coagulation cascade.**
Reproduced from Blann et al. [74]

Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischaemic tissue damage. However, once a thrombus has occurred, the aim of anticoagulant treatment is to prevent further extension of the existing clot, and to prevent secondary thromboembolic complications, which may result in serious and possibly fatal sequelae.

### 2.1.2 Pharmacokinetics and pharmacodynamics

Warfarin is a racemic mixture of 2 active isomers, the R and S forms, in roughly equal proportions. It is rapidly absorbed from the Gastro-Intestinal (GI) tract and has high bioavailability. [73] Racemic warfarin has a half-life of 36 to 42 hours, is highly bound to albumin, and the two isomers are metabolised in the liver via

different pathways. [73] The S-enantiomer is approximately 5-times more potent as a vitamin K antagonist compared to the R-isomer.

The relationship between the dose of warfarin and the response is influenced by genetic and environmental factors, including common mutations in the cytochrome P-450 enzyme responsible for oxidative metabolism of the warfarin S-isomer. [73] The cytochrome P450 (CYP450) isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2 and 3A4. [75] The principal form of human liver P450 which modulates the anticoagulant activity of warfarin is 2C9. [75] Only the unbound drug in the plasma is metabolised, thus the high protein binding characteristics of warfarin dramatically affect the total body clearance.

### 2.1.3 Monitoring anticoagulation intensity

The Prothrombin Time (PT) is the most common test used to monitor anticoagulant therapy. The PT responds to reduction in 3 of the 4 vitamin K dependent procoagulant-clotting factors (II, VII and X), which are reduced by warfarin at a rate proportionate to their respective half-lives. Thromboplastins vary in responsiveness to the anticoagulant effects of warfarin according to their source, phospholipid content, and preparation. [73] An unresponsive thromboplastin produces less prolongation of the PT for a given reduction in vitamin K dependent factors than a responsive one. The responsiveness of a thromboplastin can be measured by assessing its International Sensitivity Index (ISI). PT monitoring of warfarin is very imprecise when expressed as a PT ratio (patients value: normal control value) because of the variation in thromboplastin responsiveness. These differences in responsiveness were responsible for excessive and erratic

anticoagulation in North America in the late 1980's and early 1990's, where less responsive thromboplastins were in widespread use.

The recognition of the shortcomings in PT monitoring stimulated the development of the INR standard, and the adoption of this standard improved the monitoring, and hence the safety of anticoagulant therapy. [73]

The INR can be calculated as follows:

$$INR = (\text{patient PT/mean normal PT})^{ISI}$$

**Or** $\log INR = ISI \times (\log \text{observed PT ratio})$,

Where ISI is the international sensitivity index of the thromboplastin used to measure the PT.

Thromboplastins with recombinant tissue factor have been introduced with ISI values close to 1.0. The INR could be made more precise by using reagents with low ISI values, higher ISI values result in higher coefficients of variation. [73]

### 2.1.4 Patient specific requirements

The optimal use of warfarin has been hampered by its greater than ten-fold inter-patient variability in the doses required to attain therapeutic responses. [75] Exaggerated responses to warfarin can occur in the elderly and reflects its reduced clearance with age and also impaired clotting factor synthesis. [73] Hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of coagulation factors and elimination of warfarin. [73] Hypermetabolic states produced by fever or hyperthyroidism can increase the response to warfarin, probably due to increased catabolism of vitamin K dependent coagulation

factors. [73] Pharmacogenetic polymorphisms of CYP450 have been associated with impaired elimination of warfarin. [75]

### 2.1.5 Drug interactions

The anticoagulant response to warfarin is influenced by pharmacokinetic factors; interacting drugs may influence the pharmacokinetics of warfarin by reducing GI absorption or disrupting metabolic clearance. Stereoselective interactions may affect metabolism of either the R- or S-isomer of warfarin, inhibition of S-warfarin metabolism is more important.

Drugs such as aspirin, clopidogrel, dipyridamole, and non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of warfarin associated bleeding by inhibiting platelet function. [73] Aspirin and NSAIDs can also produce gastric erosions that increase the risk of upper GI bleeding. The INR should be measured more regularly when any drug or herbal medicine is added or withdrawn from the regimen of a patient treated with warfarin. [73] Table 5 displays a list of important drug interactions with warfarin. [76, 77]

| Increased effect from warfarin (elevated INR) | | |
|---|---|---|
| **Medications** | | |
| Amiodarone | Anabolic steroids | Carbimazole |
| Celecoxib | Cimetidine | Ciprofloxacin |
| Co-trimoxazole | Dextropropoxyphene | Disulfiram |
| Erthromycin and other macrolides | Fluconazole | Flutamide |
| Gemfibrozil | Ketoconazole | Itraconazole |
| Metronidazole | Miconazole | Nilutamide |
| Norfloxacin | Omeprazole | Phenytoin |
| Paracetamol | Propylthiouracil | Quinine/Quinidine |
| Rofecoxib | SSRIs (especially fluvoxamine or fluoxetine) | Tamoxifen |
| Tetracyclines | Thyroxine | Tramadol |
| Zafirlukast | | |
| **Herbal medicines** | | |
| Alfalfa | Aniseed | Arnica |
| Celery | Chamomile | Co-enzyme Q10 |
| Dong quai | Fenugreek | Horse chestnut |
| Prickly ash | Quassia | Red clover |
| **Decreased effect from warfarin (decreased INR)** | | |
| **Medications** | | |
| Azathioprine | Barbiturates | Carbamazepine |
| Carbimazole | Cholestyramine | Griseofulvin |
| Mercaptopurine | Phenytoin | Propylthiouracil |
| Quinidine | Quinine | Raloxifene |
| Rifabutin | Rifampicin | vitamin K (menadione, phytomenadione) |
| **Herbal medicines** | | |
| Ginseng | St John's wort | |
| **Increased bleeding risk because of effect on platelets** | | |
| **Medications** | | |
| Aspirin | Clopidogrel | Dipyridamole |
| NSAIDs | | |
| **Herbal medicines** | | |
| Feverfew | Garlic | Gingko biloba |
| Liquorice | Willow bark | |
| **Increased bleeding risk by effects on gastric mucosa** | | |
| **Medications** | | |
| Aspirin | NSAIDs/COX-2 | SSRIs |

**Table 5 Clinically important drug-drug interactions with warfarin**
Adapted from Hirsh et al. [78] and Myers. [79]

### 2.1.6 Food interactions

Patients receiving warfarin therapy are sensitive to fluctuating levels of dietary vitamin K. Health care professionals should encourage adherence to the principle of consumption of a consistent intake of foods containing vitamin K, because dose requirements will be dependant on an individual's vitamin K intake. Increased intake of dietary vitamin K sufficient to reduce the anticoagulant response to warfarin occurs in patients consuming green vegetables or vitamin K containing supplements. [73] Reduced dietary vitamin K intake potentiates the effect of warfarin; most significantly in sick patients and malnourished patients. The current daily requirement for vitamin K is 1μg/kg body weight. Vitamin K can overcome the disruption of the vitamin cycle associated with warfarin by generating the active hydroquinone cofactor through a warfarin insensitive pyridine nucleotide dependent pathway and also by displacing warfarin (competitive binding) from the binding sites. It has been demonstrated that as little as 0.5mg of vitamin K is effective in reversing anticoagulant warfarin therapy. [80]

The literature suggests that most adults consume intakes of vitamin K in the range of 60-200μg/day, [81] but vitamin K intakes of 600μg/day or more have been reported in some individuals. [81] Of all the fat-soluble vitamins, vitamin K has the highest individual daily variation in both dietary intake and corresponding plasma concentrations, [81] which increases the risk of complications through poor anticoagulant control. Although dark green vegetables are the highest contributors of vitamin K, they are not consistently consumed on a daily basis by a substantial proportion of the population.

The vitamin K concentrations of plant leaves are strongly correlated to their chlorophyll content, a general rule of thumb is that the greener the plant, the higher the vitamin K content. [81] Freezing, boiling, steaming, or microwaving vegetables does not significantly change the vitamin K content. [81] Fresh herbs are also rich sources of vitamin K, but their dietary contribution is not significant when consumed in small quantities.

The other primary dietary sources of vitamin K are four plant oils: soybean, canola, cottonseed, and olive. Salad dressings, margarines, mayonnaise, cakes and pastries may be rich in vitamin K if prepared with any of these four oils. [81] In contrast, peanut, corn, safflower, and sesame oils have a very low vitamin K content. [81]

The vitamin K content of most other foods is very low. Root vegetables, such as potatoes, onions and squash, are poor sources of vitamin K. As a general rule, animal products are also poor dietary sources of vitamin K, including dairy products and liver. However, the addition of vitamin K-rich oils to meats and eggs will increase the dietary intakes of vitamin K. [81] Table 6 displays common foods that have a vitamin K content of 10μg or more per serve. [81]

Many clinical reports attribute a dietary vitamin K-warfarin interaction to diets designed for weight loss, which are often self prescribed after warfarin therapy has been initiated and stabilised. Warfarin antagonism, or underanticoagulation, has been reported when patients started on weight-loss diets that promoted green leafy vegetables. [81]

The recommended daily allowance of 1μg/kg of vitamin K is based on coagulation factor function. Substantially higher recommended daily doses are being suggested as a result of findings that the requirement for vitamin K is

greater for the extra-hepatic vitamin K-dependent proteins, including those found in bone. [82] Thus, the approach of restricting vitamin K intake to improve stability of anticoagulant control is not appropriate to maintain optimal function of vitamin K-dependent proteins, and could lead to deficiencies of other nutrients such as carotenoids found in the same foods. [83]

| Food | Serving Size | Mean vitamin K content per serve (μg) |
|---|---|---|
| Collards, fresh/frozen, boiled | ½ Cup | 374.0 |
| Spinach, fresh/frozen, boiled | ½ Cup | 324.0 |
| Brussel sprouts, fresh/frozen, boiled | ½ Cup | 225.0 |
| Coleslaw with dressing | 1 Cup | 119.0 |
| Broccoli, fresh/frozen, boiled | ½ Cup | 88.0 |
| Cabbage, fresh, boiled | ½ Cup | 73.0 |
| Asparagus, fresh/frozen, boiled | ½ Cup | 72.0 |
| Okra, fresh/frozen, boiled | ½ Cup | 32.0 |
| Iceberg lettuce, raw | 1/6 Medium head | 28.0 |
| Tuna canned in oil, drained | 100 grams | 25.0 |
| Green peas, fresh/frozen, boiled | ½ Cup | 19.0 |
| Celery, raw | 1 Medium stalk | 17.0 |
| Mixed vegetables, frozen, boiled | ½ Cup | 15.0 |
| Sauerkraut, canned | ½ Cup | 15.0 |
| French salad dressing, regular | 2 Tablespoons | 15.0 |
| Apple pie, fresh/frozen, commercial | 1 Slice | 14.0 |
| Carrot, fresh, boiled | 1 Medium | 12.0 |
| Cauliflower, fresh, boiled | ½ Cup | 12.0 |
| Grapes, red/green, seedless, raw | ½ Cup | 12.0 |
| Plums, raw | 2 Medium | 11.0 |
| Green beans, fresh/frozen, boiled | ½ Cup | 10.0 |

**Table 6 Vitamin K content of commonly consumed foods having ≥10μg vitamin K per serve**
Adapted from Booth and Centurelli. [81]

### 2.1.7 Indications for anticoagulation

*2.1.7.1 Treatment of venous thromboembolism*

Treatment regimens for Deep Vein Thrombosis (DVT) and PE are similar because the two conditions are commonly considered manifestations of the same disease process. The optimum duration of oral anticoagulant therapy is influenced by the competing risks of bleeding and recurrent venous thromboembolism (VTE). The risk of recurrent thromboembolism when anticoagulant therapy is discontinued depends on whether the thrombosis is unprovoked (idiopathic) or is secondary to a reversible cause; a longer course of therapy is warranted when thrombosis is idiopathic or associated with a continuing risk factor. [84-87] Table 7 displays risk factors and conditions that may predispose to VTE. The reported risk of recurrence in patients with idiopathic proximal vein thrombosis has been reported to be between 10% and 27% when anticoagulants are discontinued after 3 months. [84, 85, 87] Extending therapy beyond 6 months seems to reduce the risk of recurrence to 7% during the year after treatment is discontinued. [88]

Patients should generally be treated with anticoagulants for a minimum of 3 months. Moderate-intensity anticoagulation (INR 2.0 to 3.0) has been shown to be as effective as a more intense regimen (INR 3.0 to 4.5) and is also associated with less bleeding. [89] Treatment should be longer in patients with proximal vein thrombosis than in those with distal thrombosis and in patients with recurrent thrombosis versus those with an isolated episode. Laboratory evidence of thrombophilia also may warrant a longer duration of anticoagulant therapy. Indefinite anticoagulant therapy should be considered in patients with >1 episode of idiopathic proximal vein thrombosis, thrombosis complicating malignancy, or idiopathic venous thrombosis and homozygous factor V Leiden genotype, the

antiphospholipid antibody syndrome, or deficiencies of antithrombin III, protein C, or protein S. [90-92]

- History of venous thromboembolism
- Surgery, particularly lower limb orthopaedic operations, and major pelvic or abdominal operations
- Trauma: For example, hip fractures and acute spinal injury
- Prolonged immobility
- Prolonged confinement to bed or lower limb paralysis
- Cancer, especially metastatic adenocarcinomas
- Major medical illnesses such as AMI, ischaemic stroke, CCF, acute respiratory failure
- Oestrogen use in pharmacological doses: For example, oral contraception pills, hormone replacement therapy
- Obesity
- Inherited hypercoaguable states: Activated protein C resistance (factor V Leiden mutation), protein C deficiency, protein S deficiency, antithrombin deficiency, prothrombin gene mutation
- Aquired hypercoagulable states: Lupus anticoagulant and antiphospholipid antibodies, hyperhomocysteinaemia, dysfibrinogenaemia, myeloproliferative disorders such as polycythaemia rubra vera
- Age >40 years

**Table 7 Risk factors and conditions predisposing to VTE**
Adapted from Turpie et al. [93]

It was recently found by Agnelli et al. [85] studying patients with idiopathic DVT, that the clinical benefit associated with extending the duration of anticoagulant therapy to one year, reduced the recurrence of DVT to 0.7% in the anticoagulant group compared with 8.3% in the discontinuation group. This, however, was not maintained after the therapy was discontinued in the anticoagulant group. When follow-up was continued to at least two years the rate of recurrent VTE was 15.7% and 15.8%, respectively.

*2.1.7.2 Prevention of ischaemic coronary events*

Effectiveness of oral anticoagulants in the long-term management of patients with a history of AMI is supported by the results of a meta-analysis of data pooled from 7 randomised trials published between 1964 and 1980, which showed that oral anticoagulants reduced the combined end points of mortality and nonfatal reinfarction by ≈ 20% during treatment periods of between 1 and 6 years. [94] From the results of clinical trials, the following conclusions can be drawn about long-term treatment of patients with acute myocardial ischaemia: [73]

1. High-intensity oral anticoagulation (INR ≈ 3.0 to 4.0) is more effective than aspirin but is associated with more bleeding;
2. The combination of aspirin and moderate-intensity warfarin (INR 2.0 to 3) is more effective than aspirin but is associated with a greater risk of bleeding;
3. The combination of aspirin and moderate-intensity warfarin (INR 2.0 to 3.0) is as effective as high-intensity warfarin and is associated with a similar risk of bleeding;
4. The contemporary trials have not addressed the effectiveness of moderate-intensity warfarin (INR 2.0 to 3.0), and in the absence of direct evidence, it cannot be assumed that moderate-intensity warfarin is any more effective than aspirin in preventing death or reinfarction; and
5. There is no evidence that the combination of aspirin and low-intensity warfarin (INR < 2.0) is more effective than aspirin alone, despite the fact that the combination produces more bleeding.

Therefore, the choice for long-term management involves aspirin alone, aspirin plus moderate-intensity warfarin (INR 2.0 to 3.0), or high-intensity warfarin (INR 3.0 to 4.0). The latter 2 regimens are more effective than aspirin but are associated with more bleeding and are much less convenient to administer.[73]

*2.1.7.3 Prosthetic heart valves*

The type, number, location of the prosthetic valve and risk factors for systemic embolism need to be considered when deciding on the use of anticoagulation therapy (Figure 7 displays types of valves). Risk factors that increase the incidence of systemic embolism should be considered when deciding the need to start antithrombotic therapy. These include age, smoking, hypertension, diabetes, hyperlipidaemia, presence of AF, CCF or low cardiac output, size of the LA, previous thromboembolism and abnormalities of the coagulation system. [95]

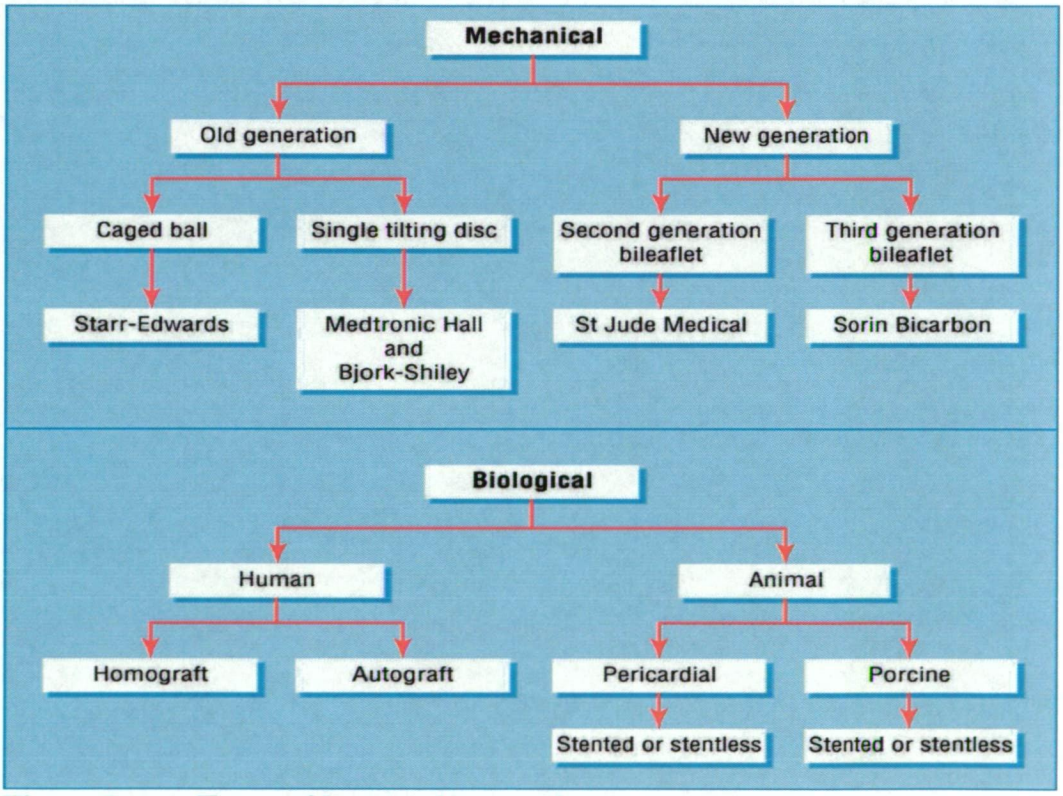



**Figure 7 Types of heart valve prostheses.**
Reproduced from Goldsmith et al. [95]

Mechanical valves are more thrombogenic than bioprosthetic valves (Table 8 for thrombogenicity) and patients with mechanical valves require lifelong anticoagulant treatment. Patients with porcine or pericardial

bioprostheses may be started on lifelong antiplatelet treatment with low dose aspirin as soon as possible after surgery. The risk of embolism is greater with a valve in the mitral position (mechanical or biological) compared with a valve in the aortic position. With either type of prosthesis or valve location, the risk of emboli is probably higher in the first few days and months after valve insertion, before the valve is fully endothelialised. Because of an increased risk of thromboemboli in the first 3 months after implantation of a biological prosthetic valve, anticoagulation with warfarin is usually recommended. [95]

| Type of valve | Model | Thrombogenicity |
|---|---|---|
| | **Mechanical** | |
| Caged ball | Starr-Edwards | ++++ |
| Single tilting disc | Bjork-Shiley, Medtronic Hall | +++ |
| Bileaflet | St Jude Medical, Sorin Bicarbon, Carbomedics | ++ |
| | **Bioprosthetic** | |
| Heterografts | Carpentier-Edwards, Tissue Med (Aspire), Hancock II | + to ++ |
| Homografts | | + |

**Table 8 Types of prosthetic valves and thrombogenicity**
Reproduced from Goldsmith et al. [95]

### 2.1.8 Warfarin dosing protocols

The dosing of warfarin can be separated into initial and maintenance phases. An anticoagulant effect is seen within 2 to 7 days after initiating warfarin, according to the dose administered. When a rapid effect is required, heparin [unfractionated or low-molecular weight heparin, (LMWH)] should be given concomitantly with warfarin until the INR > 2.0 for at least two days. Starting doses of approximately 5mg daily usually results in an INR > 2.0 after 4 or 5 days. It has been suggested that starting doses of less than 5mg should be used in the elderly [96] and in those at

increased risk of bleeding. Roberts et al. have proposed a new age-adjusted protocol (described in Table 9) and this is endorsed by the Australian Medicines Handbook (AMH). [97] The INR is usually checked daily or second daily until the therapeutic range has been reached and sustained for two consecutive days, then 2 or 3 times weekly for 1 to 2 weeks then less often, according to the stability of the results. Once the INR has become stable, the interval of monitoring can be extended to as long as four weeks. It has been suggested that estimated maintenance doses or lower doses than are traditionally used for initiation are followed [73, 98] however, this results in a longer time to therapeutic INR and has significant impacts on hospital length of stay and associated healthcare costs.

| Day | INR | Dose (mg) according to age (years) | | | |
|---|---|---|---|---|---|
| | | **<50** | **51-65** | **66-80** | **>80** |
| **1** | **<1.4** | 10 | 9 | 7.5 | 6 |
| **2** | **≤1.5** | 10 | 9 | 7.5 | 6 |
| | **≥1.6** | 0.5 | 0.5 | 0.5 | 0.5 |
| **3** | **≤1.7** | 10 | 9 | 7.5 | 6 |
| | **1.8-2.3** | 5 | 4.5 | 4 | 3 |
| | **2.4-2.7** | 4 | 3.5 | 3 | 2 |
| | **2.8-3.1** | 3 | 2.5 | 2 | 1 |
| | **3.2-3.5** | 1.5 | 1.5 | 1 | 1 |
| | **3.6-4.0** | 0.5 | 0.5 | 0.5 | 0.5 |
| | **>4** | 0 | 0 | 0 | 0 |
| **4** | **≤1.5** | 10-15 | 9-14 | 7.5-11 | 6-9 |
| | **1.6** | 8 | 7 | 6 | 5 |
| | **1.7-1.8** | 7 | 6 | 5 | 4 |
| | **1.9** | 6 | 5 | 4.5 | 3.5 |
| | **2.0-2.6** | 5 | 4.5 | 4 | 3 |
| | **2.7-3.0** | 4 | 3.5 | 3 | 2.5 |
| | **3.1-3.5** | 3.5 | 3 | 2.5 | 2 |
| | **3.6-4.0** | 3 | 2.5 | 2 | 1.5 |
| | **4.1-4.5** | Omit next dose, then | | | |
| | | 1-2 | 0.5-1.5 | 0.5-1.5 | 0.5-1 |
| | **>4.5** | Nil. Hold dose | | | |

**Table 9 Age adjusted warfarin initiation protocol.**
Adapted from Roberts et al. [99]

If dose adjustments are required, frequent monitoring is needed. Recently, two other nomograms have also been proposed in the literature. These comprise loading doses of 5mg [100] (Table 10) and recently Kovacs and associates [101] (Table 11) have proposed a 10mg loading nomogram. The latter nomogram uses 10mg loading doses on days 1 and 2 of initiation and the doses are adjusted according to response on day 3. The generalisability of these protocols has been questioned, [102] therefore, these initiation schedules are generally only appropriate for patients in whom a rapid rise in INR is needed such as outpatient treatment of VTE.

| Day | INR | Warfarin dose (mg) |
|---|---|---|
| **1** | | 5 |
| **2** | | 5 |
| **3** | <1.5 | 10 |
| | 1.5-1.9 | 5 |
| | 2.0-3.0 | 2.5 |
| | >3.0 | 0 |
| **4** | <1.5 | 10 |
| | 1.5-1.9 | 7.5 |
| | 2.0-3.0 | 5 |
| | >3.0 | 0 |
| **5** | <2.0 | 10 |
| | 2.0-3.0 | 5 |
| | >3.0 | 0 |
| **6** | <1.5 | 12.5 |
| | 1.5-1.9 | 10 |
| | 2.0-3.0 | 7.5 |
| | >3.0 | 0 |

**Table 10 5-mg warfarin initiation nomogram**
Adapted from Crowther et al. [100]

| Day 3 INR | Warfarin dose on days 3 & 4 (mg) | Day 5 INR | Warfarin dose on days 5, 6 & 7 (mg) |
|---|---|---|---|
| | | <2.0 | 15, 15, 15 |
| <1.3 | 15, 15 | 2.0-3.0 | 7.5, 5, 7.5 |
| 1.3-1.4 | 10, 10 | 3.1-3.5 | 0, 5, 5 |
| | | >3.5 | 0, 0, 2.5 |
| | | <2.0 | 7.5, 7.5, 7.5 |
| 1.5-1.6 | 10, 5 | 2.0-3.0 | 5, 5, 5 |
| 1.7-1.9 | 5, 5 | 3.1-3.5 | 2.5, 2.5, 2.5 |
| | | >3.5 | 0, 2.5, 2.5 |
| | | <2.0 | 5, 5, 5 |
| 2.0-2.2 | 2.5, 2.5 | 2.0-3.0 | 2.5, 5, 2.5 |
| 2.3-3.0 | 0, 2.5 | 3.1-3.5 | 0, 2.5, 0 |
| | | >3.5 | 0, 0, 2.5 |
| | | <2.0 | 2.5, 2.5, 2.5 |
| >3.0 | 0, 0 | 2.0-3.0 | 2.5, 0, 2.5 |
| | | 3.1-4.0 | 0, 2.5, 0 |
| | | >4.0 | 0, 0, 2.5 |

**Table 11 10-mg warfarin initiation nomogram.**
Adapted from Kovacs et al. [101]

### 2.1.9 Contraindications to anticoagulation

In the absence of clear evidence or consensus statements about what disorders should be included as contraindications to anticoagulants, most research groups have adapted the exclusion criteria used in the SPAF trial. [58] These criteria included: GI or genitourinary bleeding in the previous 6 months, determined from

the medical records; a history of three or more falls in the previous year assessed at interview, or recurrent or injurious falls in the medical record of the previous year; an inability to comply with anticoagulants, judged by the family physician; excessive alcohol intake, reported on the questionnaire to be more than 28 standard units during the previous week in men and 21 units in women; blood pressure of more than 180/100 mm Hg (uncontrolled hypertension); and daily use of NSAIDs.

In a population based survey of a large cohort of patients who were aged > 65 years in northern England, standard contraindications to long-term oral anticoagulants were present in 43% of patients and irreversible contraindications were present in 26% of patients. [103] Uncontrolled hypertension and use of NSAIDs were taken as reversible, if hypertension was adequately treated or NSAIDs replaced with alternative therapy, which would allow the patient to take anticoagulants.

The Australian prescription products guide [104] lists contraindications to warfarin as:

- History of falls or tendency to fall,
- Dementia or unsupervised psychosis,
- Chronic alcoholism or tendency to abuse alcohol,
- Chronic liver disease,
- Uncontrolled hypertension,
- Blood dyscrasias (platelet count $<100*10^9/L$) or documentation of any coagulation defects (congenital or induced),
- Bleeding tendencies that increased the risk of bleeding such as peptic ulcer, diverticular disease, genitourinary tract disease, sub-acute bacterial endocarditis, pericardial effusion or cerebral haemorrhage,
- Compliance,
- History of problems with warfarin in the past (e.g. poor control of INR, allergy) and
- A comorbid condition with a poor prognosis such as malignancy.

### 2.1.10 Warfarin-related bleeding complications

#### *2.1.10.1 Bleeding risk of warfarin therapy*

The main complication of oral anticoagulant therapy is bleeding. These complications are generally classified as major if they are intracranial or retroperitoneal, if it leads directly to death or if it results in hospitalisation or transfusion. [105] Most bleeding problems are clinically minor, although patients are unlikely to view such bleeds in these terms. The problems include nosebleeds (epistaxis), bruising, and excessive bleeding after minor injury such as shaving. Patients should be made aware of these common problems and be reassured that these events are expected in patients receiving warfarin treatment. [106]

Overall, the rates of warfarin-related bleeding in the studies shown in Table 12 have been low and the rates vary according to reason for treatment. In two meta-analyses [107, 108] of 12 trials of warfarin for stroke prevention, warfarin increased the odds of major bleeding; but the absolute risk increase was only 0.3%/yr. [108] Although intracranial bleeding was more frequent in patients treated with warfarin in these trials (0.3%/yr vs 0.1%/yr in patients not treated with warfarin or aspirin), the absolute difference was small and overwhelmed by the substantial reduction in the frequency of stroke.

One study [58] (SPAF II) raised concern that the risk for warfarin-related bleeding, especially intracranial haemorrhage (ICH), may be increased substantially in patients $\geq$ 75 years old. The rate of major bleeding while receiving warfarin was 2.3%/yr, compared with 1.1%/yr for patients receiving aspirin, 325mg per day. However, the rate of major warfarin-related bleeding was 4.2%/yr in patients $\geq$ 75 years old, compared with 1.7%/yr in younger patients;

the rates for intracranial bleeding were 1.8%/yr and 0.6%/yr, respectively. The reason why these rates are substantially higher than those observed in the other clinical trials of warfarin in patients with AF is likely to be related to the intensity of anticoagulant therapy: virtually all ICH in SPAF II, as in the other clinical trials, were associated with an INR > 3.0. [58] In contrast, in the SPAF III trial (targeted INR 2.0 to 3.0), the mean age was 71 years and the rate of ICH was 0.5%/yr. [38]

| Source | Treatment | Patients, No. | Bleeding† | | Targeted INR |
|---|---|---|---|---|---|
| | | | Major | Fatal | |
| Petersen et al[70] | Warfarin | 335 | ‡ | 1 (0.3) | 2.8–4.2 |
| | ASA (75 mg) | 336 | ‡ | 0 | |
| | Placebo | 336 | ‡ | 0 | |
| SPAF[69] | Warfarin | 201 | 1.7/yr | ‡ | 2.0–3.5 |
| | ASA (325 mg) | 192 | 0.9/yr | ‡ | |
| | Placebo | 195 | 1.2/yr | ‡ | |
| Boston[68] | Warfarin | 212 | 8 (3.8) | 1 (0.5) | 1.5–2.7 |
| | No treatment | 208 | 8 (3.8) | 1 (0.5) | |
| Connolly et al[73] | Warfarin | 187 | 5 (2.7) | 2 (1.1) | 2.0–3.0 |
| | Placebo | 191 | 1 (0.5) | 0 | |
| SPAF II[71] | Warfarin ≤ 75 yr | 358 | 1.7/yr | ‡ | 2.0–4.5 |
| | ASA ≤ 75 yr | 357 | 0.9/yr | ‡ | |
| | Warfarin > 75 yr | 197 | 4.2/yr§ | ‡ | |
| | ASA > 75 yr | 188 | 1.6/yr | ‡ | |
| European[18] | Warfarin | 225 | 13 (5.8) | 3 (1.3) | 2.5–4.0 |
| | Placebo | 230 | 3 (1.3) | 1 (0.4) | |
| | ASA (300 mg) | 404 | 6 (1.5) | 2 (0.5) | |
| Ezekowitz et al[72] | Warfarin | 260 | 6 (2.3) | 0 | 1.4–2.8 |
| | Placebo | 265 | 4 (1.5) | 1 (0.4) | |
| SPAF III[74] | Warfarin plus ASA (325 mg) | 521 | 13 (2.4/yr) | 3 (0.6/yr) | 1.2–1.5 |
| | Warfarin | 523 | 12 (2.1/yr) | 2 (0.4/yr) | 2.0–3.0 |
| Morocutti et al[76] | Warfarin | 454 | 6 (1.3) | 1 (0.2) | 2.0–3.5 |
| | Indobufen | 462 | 1 (0.2) | 0 | — |
| Gullov et al[77] | Warfarin | 170 | 1.1/yr | 0.3/yr | 2.0–3.0 |
| | Warfarin (1.25 mg) | 167 | 0.8/yr | 0 | — |
| | Warfarin plus aspirin (1.25 mg and 300 mg) | 171 | 0.3/yr | 0 | — |
| | Aspirin (300 mg) | 169 | 1.4/yr | 0.3/yr | — |
| Pengo et al[75] | Warfarin | 153 | 2.6/yr | ‡ | 2.0–3.0 |
| | Warfarin (1.25 mg) | 150 | 1.0/yr | ‡ | — |
| Hellemons et al[78] | Phenprocoumon/acenocoumarol | 131 | 0.5/yr | ‡ | 2.5–3.5 |
| | Phenprocoumon/acenocoumarol | 122 | 1.4/yr | ‡ | 1.1–1.6 |
| | Aspirin (150 mg) | 141 | 1.4/yr | ‡ | — |

*Boston = The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators; European = The European Atrial Fibrillation Trial Study Group.
†Data presented as No. (%), %/yr, or No. (%/yr).
‡Not reported in publications.
§$p < 0.04$.

**Table 12 Bleeding risk from anticoagulant trials in patients with AF.** Reproduced from Levine et al. [105]

In recent meta-analyses of bleeding during oral anticoagulant therapy by Linkins, Choi and Douketis, the risk of bleeding in the first three months of therapy (2.06%) was nearly the same as that in the remaining time to one year

(2.74%). Table 13 displays major bleeding rates in a number of different studies analysed by Linkins, Choi and Douketis.

*Table 1.* **Major Bleeding Events in Patients Receiving Oral Anticoagulant Therapy***

| Study, Year (Reference) | Study Type | Patients Receiving Oral Anticoagulants | Duration of Follow-up | Major Bleeding Episodes | Case-Fatality Rate | Intracranial Bleeding Episodes | Loss to Follow-up |
|---|---|---|---|---|---|---|---|
| | | *n* | *mo* | *n* (%) | % | *n* | *n* (%) |
| Hull et al., 1990 (44) | RCT | 199 | 3 | 16 (8) | 6 | 0 | 0 |
| Prandoni et al., 1992 (53) | RCT | 170 | 3 | 8 (5) | 13 | 1 | 0 |
| Lopaciuk et al., 1992 (49) | RCT | 146 | 3 | 0 | 0 | 0 | 0 |
| Brandjes et al., 1992 (37) | RCT | 120 | 6 | 5 (4) | 0 | 0 | 0 |
| Hull et al., 1992 (57) | RCT | 432 | 3 | 17 (4) | 18 | 2 | 0 |
| Pini et al., 1994 (58) | RCT | 94 | 3 | 3 (3) | 0 | 1 | 0 |
| Levine et al., 1995 (48) | RCT | 301 | 3 | 1 (0.3) | 100 | 1 | 0 |
| Schulman et al., 1995 (6) | RCT | 454 | 6 | 5 (1) | 0 | 2 | 21 (5) |
| Lindmarker et al., 1996 (59) | Cohort | 434 | 3 | 4 (0.9) | 25 | 2 | 0 |
| Koopman et al., 1996 (46) | RCT | 400 | 3 | 5 (1) | 40 | 1 | 4 (1) |
| Das, 1996 (39) | RCT | 55 | 3 | 0 | 0 | 0 | 3 (5) |
| Bounameaux et al., 1997 (36) | RCT | 47 | 3 | 0 | 0 | 0 | 0 |
| Columbus Investigators, 1997 (34) | RCT | 1021 | 3 | 28 (3) | 7 | NA | 0 |
| Schulman et al., 1997 (7) | RCT | 227 | 6 or 48 | 11 (5) | 18 | 1 | 0 |
| Simonneau et al., 1997 (54) | RCT | 612 | 3 | 18 (3) | 17 | 1 | 0 |
| Monreal et al., 1998 (60) | Cohort | 244 | 3 or 6 | 2 (0.8) | 0 | 1 | 0 |
| Wells et al., 1998 (61) | Cohort | 194 | 3 | 4 (2) | 0 | 0 | 0 |
| Charbonnier et al., 1998 (38) | RCT | 651 | 3 | 17 (3) | 29 | 1 | 1 (0.2) |
| Decousus et al., 1998 (40) | RCT | 400 | 24 | 39 (10) | 8 | 3 | 4 (1) |
| Kovacs et al., 1998 (45) | RCT | 111 | 3 | 3 (3) | 0 | 0 | 0 |
| Leroyer et al., 1998 (47) | RCT | 223 | 3 | 7 (3) | 29 | 2 | 0 |
| Lopaciuk et al., 1999 (50) | RCT | 95 | 3 | 1 (1) | 0 | 0 | 0 |
| Gonzalez-Fajardo et al., 1999 (41) | RCT | 80 | 3 | 2 (3) | 0 | 0 | 3 (4) |
| Kearon et al., 1999 (8) | RCT | 79 | 24 | 3 (4) | 0 | 0 | 0 |
| Harenberg et al., 2000 (42) | RCT | 538 | 6 | 20 (4) | 15 | 3 | 0 |
| Boccalon et al., 2000 (35) | RCT | 201 | 6 | 4 (2) | 0 | 0 | 0 |
| Hull et al., 2000 (43) | RCT | 200 | 3 | 6 (3) | 0 | 1 | 0 |
| Rembrandt Investigators, 2000 (55) | RCT | 119 | 3 | 3 (3) | 0 | NA | 0 |
| Kovacs et al., 2000 (62) | Cohort | 108 | 3 | 3 (2) | 0 | 0 | 0 |
| Agnelli et al., 2001 (9) | RCT | 134 | 12 | 4 (3) | 0 | 0 | 0 |
| Merli et al., 2001 (51) | RCT | 900 | 3 | 15 (2) | 47 | NA | 2 (0.2) |
| Pinede et al., 2001 (52) | RCT | 631 | 3 or 6 | 15 (2) | 7 | 1 | 0 |
| Breddin et al., 2001 (56) | RCT | 1137 | 3 | 7 (0.6) | 0 | 0 | 0 |
| Total | | 10 757 | | 276 | | 24 | 38 |

* NA = not available; RCT = randomized, controlled trial.

**Table 13 Bleeding events in patients receiving oral anticoagulant therapy.** Reproduced from Linkins, Choi and Douketis. [109]

### *2.1.10.2 Relationship to the INR*

The safety and efficacy of warfarin depends on maintaining the INR within the therapeutic range as displayed in Figure 8. Analysis of primary prevention trials for stroke prevention in AF, found that a large number of thromboembolic and bleeding events occurred when the INR was outside of the therapeutic range. [110]

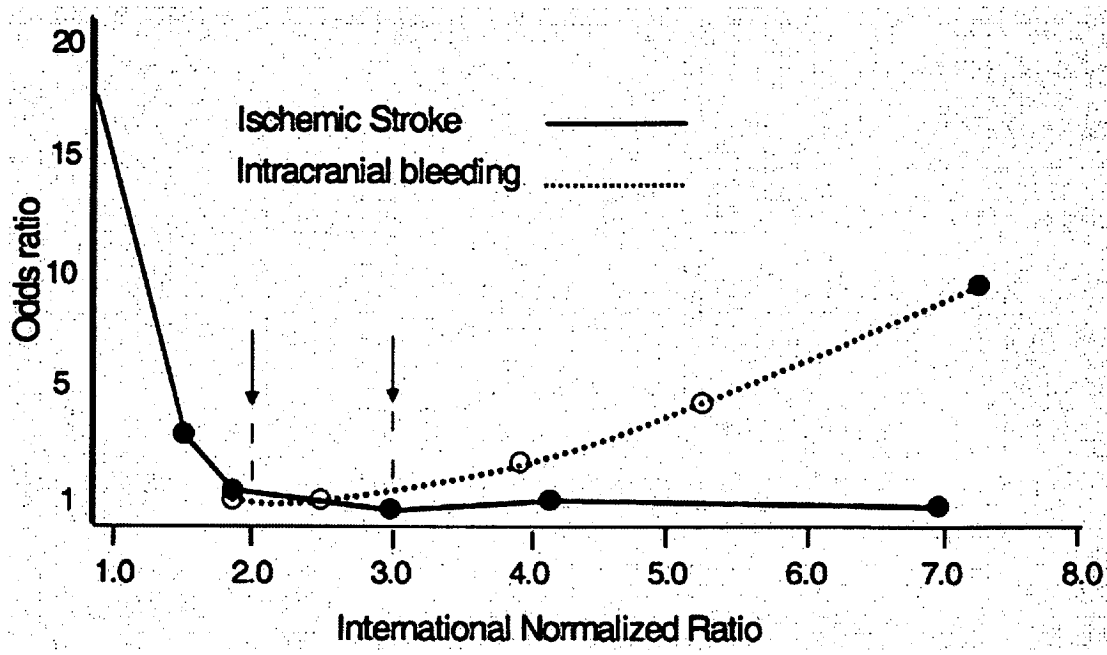



**Figure 8 Adjusted odds ratios for ischaemic stroke and intracranial bleeding in relation to intensity of anticoagulation in randomised trials of antithrombotic therapy for patients with AF.**
Reproduced from Hylek et al. [111]

Analysis of other cohort studies have shown a sharp increase in the risk of bleeding when the INR is higher than the upper limit of the therapeutic range [112-114] and the risk of thromboembolism is increased when the INR falls below 2.0. [38, 111] A recent study showed an excess mortality from all causes with increased INR as shown in Figure 9. [115]

In randomised clinical trials for DVT and mechanical heart valves, the frequency of major bleeding in patients randomly assigned to less intense warfarin therapy (INR approximately 2.0 to 3.0) has been less than half the frequency in patients randomly assigned to more intense warfarin therapy (targeted INR > 3.0). [105] The intensity of anticoagulant effect is probably the most important risk factor for ICH, independent of the indication for therapy, with the risk increasing dramatically with an INR > 4.0. [110]

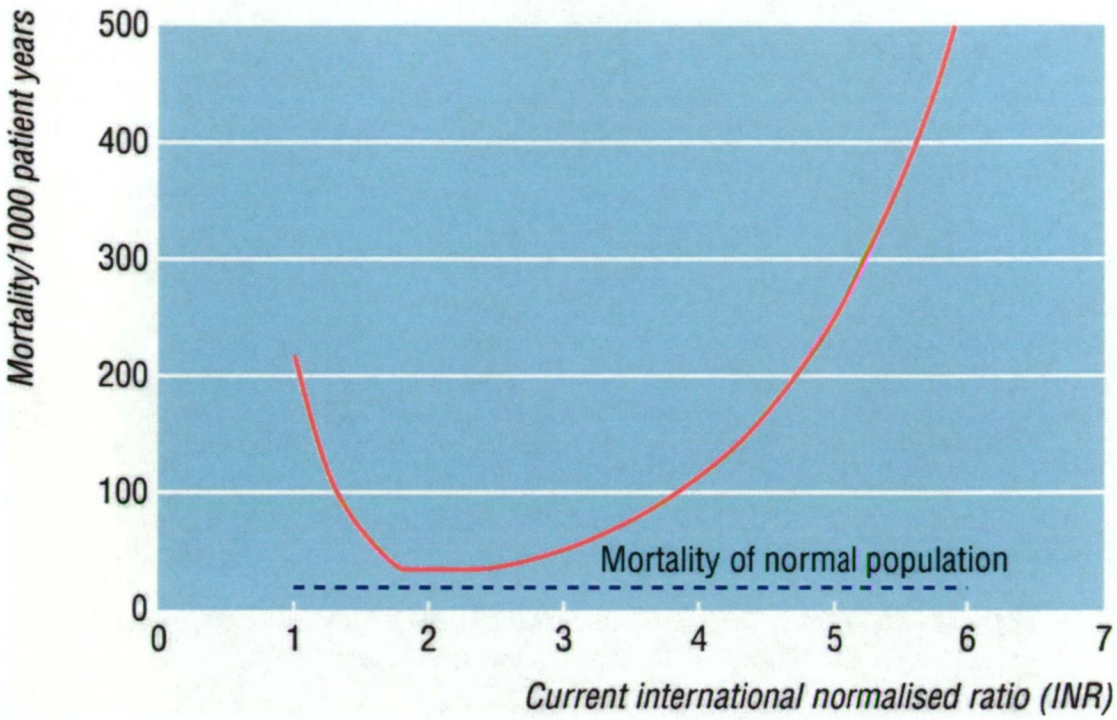



**Figure 9 Risk of death associated with different levels of anticoagulation.** Reproduced from Oden et al. [115]

The incidence of major bleeding from five randomised trials for AF was 1.3% for warfarin (INR 2.0 to 3.0), compared to 1.0% with placebo. [36] Increased variation in the INR is associated with an increased frequency of haemorrhage independent of the mean INR. [116, 117] This effect is probably attributable to increased frequency and degree of marked elevations in the INR.

The cumulative risk of bleeding is directly related to the length of anticoagulant therapy. A number of studies have reported that the risk of bleeding associated with warfarin is highest early in the course of therapy. [105, 116, 118-120] In one of these studies, for example, the frequency of major bleeding decreased from 3.0% during the first month of outpatient warfarin therapy to 0.8% per month during the rest of the first year of therapy and to 0.3% per month thereafter. [121]

### 2.1.10.3 *Risk factors and predictors of bleeding*

Contributing factors to the risk of bleeding are the underlying clinical disorders [89, 122-125] and concomitant use of aspirin, NSAIDs or other drugs that impair platelet function, produce gastric erosions or impair synthesis of vitamin K dependent clotting factors. A validated bleeding index showed that the risk of major bleeding is also related to age > 65 years, a history of stroke or GI bleeding, and comorbid conditions such as renal insufficiency or anaemia. [89, 122] Importantly, these risk factors were considered additive; patients with 2 or 3 risk factors had a much higher incidence of warfarin associated bleeding than those with none or one. The cumulative incidence of major bleeding at 48 months was 53% in high-risk patients (three or four risk factors), 12% in middle-risk patients (one or two risk factors), and 3% in low-risk patients (no risk factors).

Kuijer et al. [126] recently developed another prediction model based on age, gender, and the presence of malignancy. In patients classified at high, middle, and low risk, the frequency of major bleeding was 7%, 4%, and 1%, respectively after 3 months of therapy. [127] The elderly are more prone to bleeding even after controlling for anticoagulation intensity. [110] Bleeding that occurs at an INR of < 3.0 is frequently associated with trauma or an underlying lesion in the GI or urinary tract. [89]

In at least eight separate clinical studies, possession of the CYP2C9*2 or CYP2C9*3 variant alleles, which result in decreased enzyme activity, has been associated with a significant decrease in a mean warfarin dose requirement. [128] Aithal et al. [129] in a case-control study showed a significant relationship with variant alleles of the CYP2C9 enzyme and low warfarin dose requirement compared to patients higher dose requirements. Furthermore patients in the low-

dose requirement group were more likely to have difficulties at the time of induction of warfarin therapy and to have an increased risk of major bleeding complications. A recent review of the relationship between CYP2C9 and warfarin dose stated, "relationships between CYP2C9 genotype, enzyme activity, metabolism of probe substrates, dosage requirements and bleeding complications should be interpreted with caution, and further studies are required". [75]

#### *2.1.10.4 Managing elevated INR or warfarin associated bleeding*

A number of approaches can be undertaken to lower an elevated INR. The first step is to stop or withhold warfarin; the next step can be to administer vitamin K and the third and most effective way is to infuse fresh frozen plasma (FFP) or prothrombin concentrate, which is highly expensive. After warfarin is withheld, the INR falls over several days (an INR between 2.0 and 3.0 falls to the normal range 4 to 5 days after warfarin is stopped). [130] The INR declines substantially within 24 hours after treatment with vitamin K. [131]

Even when the INR is elevated, the absolute daily risk of bleeding is low. This leads many physicians to manage patients with INR levels as high as 5 to 10 by withholding warfarin, unless the patient is at very high risk of bleeding or bleeding has already developed. Oral vitamin K is the treatment of choice unless very rapid reversal of anticoagulation is critical, when vitamin K can be administered by slow intravenous (IV) infusion (5 to 10 mg over 30 minutes). The anticoagulant reversal effect is mediated by vitamin K through another quinone reductase, [73] which is operative at high tissue concentrations of vitamin K, and is not inhibited by warfarin. In 2001, the American College of Chest Physicians [132]

published the following recommendations for managing patients on coumarin anticoagulants who need their INRs lowered because of either actual or potential bleeding.

- When the INR is above the therapeutic range but < 5, and the patient has not developed clinically significant bleeding, and rapid reversal is not required for surgical intervention, the dose of warfarin can be reduced or the next dose omitted and resumed (at a lower dose) when the INR approaches the desired range.

- If the INR is between 5 and 9 and the patient is not bleeding and has no risk factors that predispose to bleeding, the next 1 or 2 doses of warfarin can be omitted and warfarin reinstated at a lower dose when the INR falls into the therapeutic range. Alternatively, the next dose of warfarin may be omitted and vitamin K (1 to 2.5 mg) given orally. This approach should be used if the patient is at increased risk of bleeding.

- When more rapid reversal is required to allow urgent surgery or dental extraction, vitamin K can be given orally in a dose of 2 to 5 mg, anticipating reduction of the INR within 24 hours. An additional dose of 1 or 2 mg vitamin K can be given if the INR remains high after 24 hours.

- If the INR is > 9 but clinically significant bleeding has not occurred, vitamin K, 3 to 5 mg, should be given orally, anticipating that the INR will fall within 24 to 48 hours. The INR should be monitored closely and vitamin K repeated as necessary.

- When rapid reversal of anticoagulation is required because of serious bleeding or major warfarin overdose (e.g., INR > 20), vitamin K should be given by slow IV infusion in a dose of 10 mg, supplemented with transfusion of fresh plasma or prothrombin complex concentrate, according to the urgency of the situation. It may be necessary to give additional doses of vitamin K every 12 hours.

- In cases of life-threatening bleeding or serious warfarin overdose, prothrombin complex concentrate replacement therapy is indicated, supplemented with 10 mg of vitamin K by slow IV infusion; this can be repeated, according to the INR. If warfarin is to be resumed after administration of high doses of vitamin K, then heparin can be given until the effects of vitamin K have been reversed and the patient again becomes responsive to warfarin.

### *2.1.10.5 Perioperative management of anticoagulation*

The management of patients treated with warfarin when there are events that require the interruption of anticoagulation can be troublesome. Most patients can undergo dental procedures, arthrocentesis, cataract surgery, and diagnostic endoscopy without alteration of their regimen. [133] For other invasive and surgical procedures, oral anticoagulation needs to be withheld, and the decision whether to pursue an aggressive strategy of perioperative administration of IV heparin or subcutaneous LMWH should be individualised as suggested in Table 14.

| Indication for anticoagulation | Examples | Recommendation |
|---|---|---|
| Indication with low annual risk of thromboembolic stroke (<4%) without anticoagulation | AF without history of thromboembolic stroke | Withhold oral anticoagulation |
| Indication with moderate annual risk of thromboembolic stroke (4%-7%) without anticoagulation | Mechanical aortic valve | Withhold oral anticoagulation. Optional administration of either treatment dose of IV heparin or SC LMWH whilst INR is sub-therapeutic |
| Indication with high annual risk of thromboembolic stroke (>7%) without anticoagulation | Mechanical mitral valve; AF with history of thromboembolic stroke | Withhold oral anticoagulation and administer either treatment dose of IV heparin or treatment dose of SC LMWH whilst INR is sub-therapeutic |

**Table 14 Guidelines for the perioperative management of anticoagulation**
Adapted from Dunn et al. [133]

## 2.2 Antiplatelets

### 2.2.1 Aspirin

Aspirin (or acetylsalicylic acid) irreversibly inhibits cyclooxygenase-1 (COX-1) (Figure 10) in platelets and megakaryocytes and thereby blocks the formation of thromboxane $A_2$ ($TXA_2$), which is a potent vasoconstrictor and platelet aggregant. [134] Because platelets are unable to regenerate COX, the immediate antithombotic effect of aspirin remains for the lifespan of the platelet (8-10 days). After stopping aspirin therapy, normal haemostasis may be regained when about 20% of platelets have normal COX activity; therefore daily aspirin intake is recommended.

Aspirin is readily absorbed from the GI tract, with peak concentrations achieved in 30-40 minutes. When given as a single oral dose, at least 160mg of soluble aspirin is required to maximally inhibit platelet function within 30 minutes. [135] Soluble and enteric-coated aspirin have a cumulative effect, so that platelet $TXA_2$ formation is maximally inhibited after 4-5 days. [135] The evidence from randomised controlled trials supports daily doses of aspirin in the range 75–150 mg for the long-term prevention of serious vascular events in high-risk patients. [136] Higher doses of 500–1500 mg aspirin daily are no more effective than lower doses. [136]

Aspirin use is associated with dose-related symptoms of upper-GI toxicity (nausea, heartburn, epigastric pain). High doses of aspirin (500–1500 mg daily), compared with medium (75–325 mg daily) or low (30 mg) doses, significantly increase the risk of upper-GI symptoms [135] Enteric-coated aspirin may cause less gastric irritation than soluble aspirin. [135]

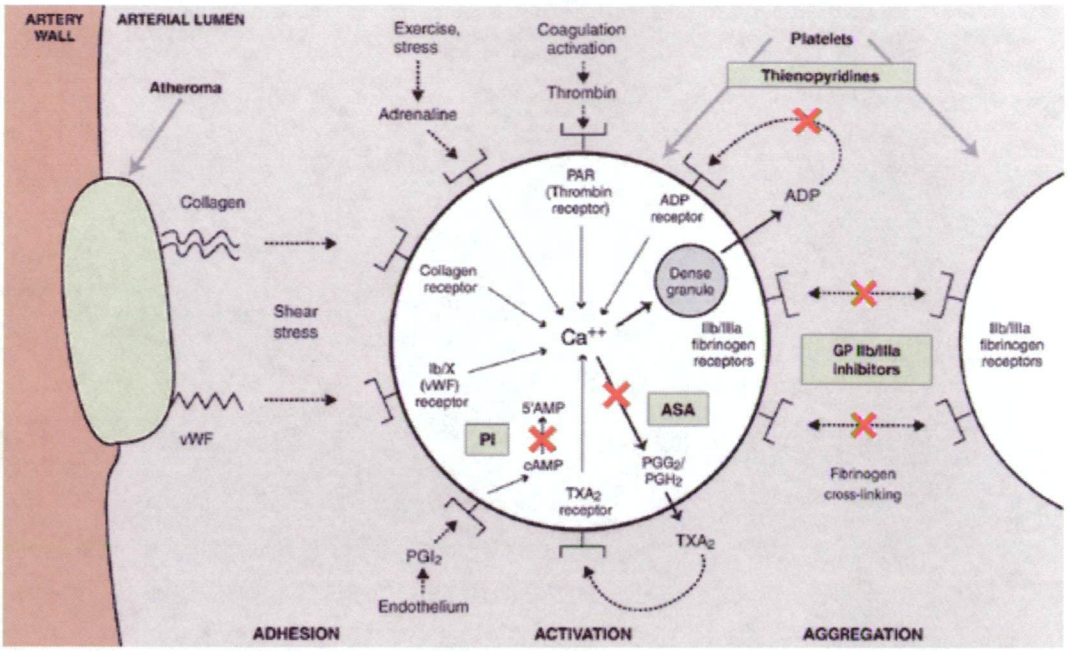



**Figure 10 Pivotal roles of platelets in thrombosis and the sites of action of currently approved antiplatelet drugs.**

Adhesion of platelets to proteins (collagen, von Willebrand factor), particularly under conditions of high shear stress, and the action of platelet agonists (adrenaline, thrombin, ADP, thromboxane $A_2$) leads to the mobilisation of calcium ion (Ca++), which functions as a mediator of platelet activation. Aspirin inhibits thromboxane A2 synthesis by irreversibly acetylating cyclooxygenase-1; the thienopyridines (clopidogrel, ticlopidine) irreversibly block the ADP receptor; and glycoprotein IIb/IIIa inhibitors block the final common pathway of platelet activation leading to fibrinogen cross-linking of platelets and platelet aggregation. Phosphodiesterase inhibitors (dipyridamole, cilostazol) elevate intracellular cyclic AMP levels and thereby inhibit platelet function. Abbreviations: ADP=adenosine diphosphate; ASA=aspirin; cAMP=cyclic adenosine monophosphate; GP=glycoprotein; PGG2=prostaglandin G2; PAR=Protease activated receptor; PGH2=prostaglandin H2; PGI2=prostacyclin; PI=phosphodiesterase inhibitor; TXA2=thromboxane A2; vWF=von Willebrand factor.
Reproduced from Hankey and Eikelboom. [135]

Aspirin is associated with about a 60%–70% relative increase in risk of non-fatal extracranial haemorrhage (mostly from the GI tract), which corresponds to an absolute excess risk of about one to two per 1000 patients treated per year. [136, 137] Aspirin is associated with an increased risk of ICH of about one per 1000 patients treated for 3 years. [138]

### 2.2.2 ADP-receptor antagonists

The thienopyridine derivatives (clopidogrel and ticlopidine) are metabolised in the liver to active compounds, which covalently bind to the adenosine phosphate (ADP) receptor on platelets and dramatically reduce platelet activation (Figure 10). Repeated daily oral doses of 75 mg clopidogrel are required to achieve a steady-state maximal platelet inhibition, which is comparable with that produced by 250mg ticlopidine orally, twice daily. [60] Compared with aspirin, the thienopyridines are associated with a lower risk of GI haemorrhage and upper-GI symptoms and an increased risk of diarrhoea and skin rash. Clopidogrel has replaced ticlopidine because the latter is associated with an excess of neutropaenia compared with aspirin particularly in the early months of therapy, whereas clopidogrel is not. [139] Furthermore, ticlopidine is associated with significant excess of thrombocytopaenia and of thrombotic thrombocytopaenic purpura. [135] If ticlopidine is to be used, haematological monitoring should be undertaken at commencement and every 2 weeks in the first 4 months of therapy. [135]

## 2.3 Antithrombotics for stroke prevention

### 2.3.1 Clinical trials of antithrombotic therapies

Before 1990, antithrombotic therapy for prevention of ischaemic stroke in AF was mainly limited to those patients with rheumatic (valvular) heart disease and or prosthetic heart valves. [10] Anticoagulation was also only accepted therapy for patients who had sustained an ischaemic stroke, and was only advocated for other groups of patients such as those with CCF and concomitant AF. Five large randomised trials published between 1989 and 1992 evaluated oral anticoagulation, and 2 tested aspirin for primary prevention of thromboembolism in NVAF. [140-143] A sixth trial focused on secondary prevention among patients who had survived nondisabling stroke or TIA. [39]

Table 15 displays all antithrombotic treatment trials for stroke prevention in AF. [38, 39, 58, 140-150] All of the listed trials excluded patients considered at high risk of bleeding. Recommendations from the AHA/ACC/ESC are that:

> "Antithrombotic therapy (oral anticoagulation or aspirin) should be offered to all patients with AF to prevent thromboembolism". [1]

| Trials | Reference | Year Published | No. of Patients | Interventions |
|---|---|---|---|---|
| Large Published Trials | | | | |
| Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation I (AFASAK I) | 468 | 1989 | 1,007 | OA, ASA, placebo |
| Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation II (AFASAK II) | 487 | 1998 | 677 | OA, ASA, OA*+ASA, OA* |
| Stroke Prevention in Atrial Fibrillation I (SPAF I) | 32 | 1991 | 1,330 | OA, ASA, placebo |
| Stroke Prevention in Atrial Fibrillation II (SPAF II) | 488 | 1994 | 1,100 | OA, ASA |
| Stroke Prevention in Atrial Fibrillation III (SPAF III) | 438 | 1996 | 1,044 | OA, OA*+ASA |
| Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) | 456 | 1990 | 420 | OA, control |
| Canadian Atrial Fibrillation Anticoagulation (CAFA) | 489 | 1991 | 378 | OA, placebo |
| Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) | 469 | 1992 | 571 | OA, placebo |
| European Atrial Fibrillation Trial (EAFT) | 439 | 1993 | 1,007 | OA, ASA, placebo |
| Studio Italiano Fibrillazione Atriale (SIFA) | 490 | 1997 | 916 | OA, indobufen |
| Minidose Warfarin in Nonrheumatic Atrial Fibrillation | 491 | 1998 | 303 | OA, OA* |
| Prevention of Arterial Thromboembolism in Atrial Fibrillation (PATAF) | 461 | 1999 | 729 | OA, OA*, ASA |
| Small or pilot trials | | | | |
| Harenberg et al. | 492 | 1993 | 75 | LMW heparin, control |
| Low-dose Aspirin, Stroke, Atrial Fibrillation (LASAF) | 493 | 1996 | 285 | ASA, placebo |
| Subgroups with AF in other trials | | | | |
| European Stroke Prevention Study II (ESPS II) | 494 | 1997 | 429 | ASA, dipyridamole, placebo |
| Ongoing or unpublished AF trials | | | | |
| French Aspirin Coumarin Collaborative Study | | ... | ... | OA, OA+ASA |
| Swedish Atrial Fibrillation Trial | | ... | ... | ... |
| Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) | | ... | ... | OA, thrombin inhibitor |

AF indicates atrial fibrillation; OA, oral anticoagulation; OA*, low-dose oral anticoagulation; ASA, aspirin; LMW, low-molecular-weight.
Adapted with permission from Hart et al. (460) Ann Intern Med 1999;131:492-501. (The American College of Physicians-American Society of Internal Medicine is not responsible for the accuracy of the translation.)

**Table 15 Randomised trials of antithrombotic therapy in patients with AF.** Adapted from ACC/AHA/ESC guidelines for the management of patients with AF [1]

### 2.3.2 Warfarin

Five trials with relatively similar study designs have addressed anticoagulant therapy for primary prevention of ischaemic stroke in patients with NVAF. The SPAF study, the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), [141] and the Stroke Prevention In Nonvalvular Atrial Fibrillation (SPINAF) [143] trial were carried out in the United States; the Atrial Fibrillation, Aspirin, Anticoagulation study (AFASAK) [142] was carried out in Denmark; and the Canadian Atrial Fibrillation Anticoagulation (CAFA) study [145] was stopped before completion because of convincing results in 3 of the other trials. [36]

Meta-analyses [151] according to intention to treat principle showed that adjusted dose oral anticoagulation is highly efficacious for prevention of stroke, with a risk reduction of 62% (95% CI 48% to 72%) vs placebo as displayed in

Figure 11. The reduction was similar for both primary and secondary prevention and for both disabling and non-disabling strokes. Excluding patients not undergoing oral anticoagulation at the time of stroke, the efficacy exceeded 80%, which corresponds to a reduction of the 5-fold risk of stroke back to the 1-fold baseline risk without AF. [152] In most areas of therapeutics, relative improvements in the range of 25% are considered outstanding. [153] Meta-analyses have also shown that the stroke risk reduction offered by warfarin compared to aspirin is 36% (95% CI 14% to 52%) as shown in Figure 12.

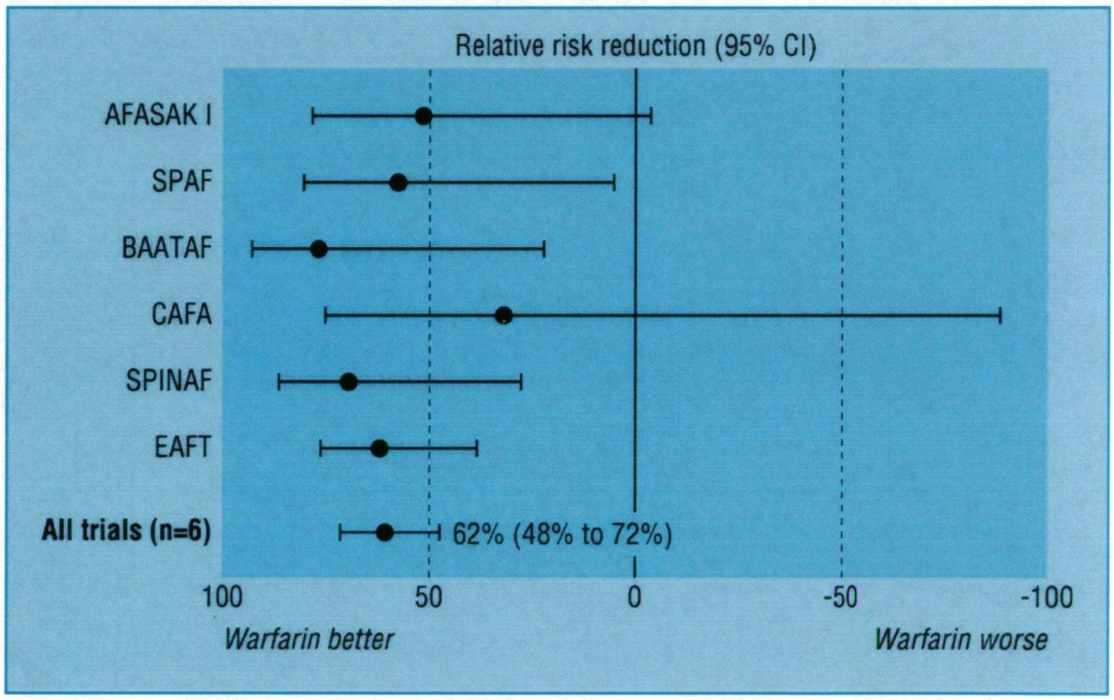



**Figure 11 Antithrombotic therapy for stroke prevention in AF: Adjusted-dose warfarin compared with placebo.**
Reproduced from Lip et al. [154]

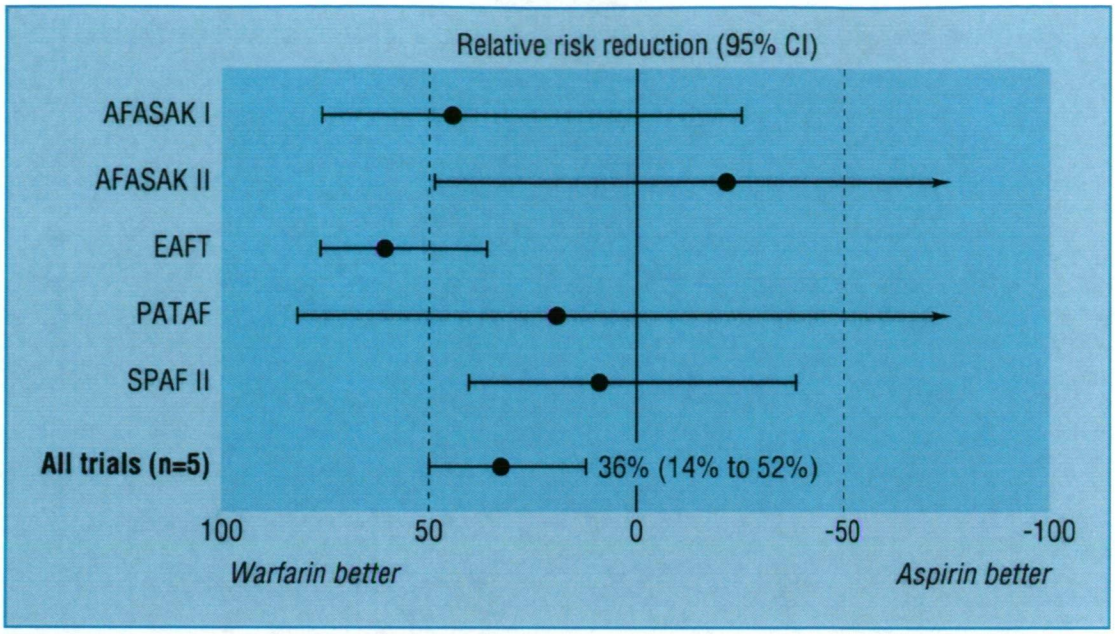



**Figure 12 Antithrombotic therapy for stroke prevention in AF: Warfarin compared with aspirin.**
Reproduced from Lip et al. [154]

Oral anticoagulation may be most beneficial for AF patients at high thromboembolic risk, offering only modest reduction over aspirin in both the relative and absolute rates of stroke for AF patients at low risk. Recent recommendations from the AHA/ACC/ESC suggest the following:

> "Anticoagulation adjusted to achieve an INR of 2.0 to 3.0 in patients at high risk of stroke unless contraindicated, and the selection of antithrombotic therapy should be irrespective of the type of AF". [1]

### 2.3.3 Optimal intensity of anticoagulation

The target intensity of anticoagulation involves a balance between prevention of ischaemic stroke and avoidance of haemorrhagic complications. Targeting the lowest intensity of anticoagulation to minimise the risk of bleeding is particularly important for elderly AF patients. Maximum protection against stroke in AF is

probably achieved with an INR range of 2.0 to 3.0, [38, 111, 113] whereas an INR range of 1.6 to 2.5 appears to be associated with incomplete efficacy, estimated at approximately 80% of that achieved with higher-intensity anticoagulation. [111]

Two randomised trials with a target INR of 1.4 to 2.8 (estimated mean INR achieved 2.0 to 2.1) found the largest relative risk reduction (RRR) for ischaemic stroke. For primary prevention in most AF patients under 75 years of age and for secondary prevention, an INR of 2.5 (target range 2.0 to 3.0) is recommended. [1] A target INR of 2.0 (target range 1.6 to 2.5) is reasonable for primary prevention in those patients aged over 75 years. [1] In clinical trials, INRs achieved were more often below than above the target range.

### 2.3.4 Secondary prevention

The reduction in relative risk with warfarin applies equally to primary and secondary prevention but, as history of stroke confers an increased annual stroke risk (12% *versus* 4.5%), the absolute risk reduction (ARR) is greater for secondary prevention. The number of patients with AF needing treatment with warfarin to prevent one stroke is therefore about three times greater in primary prevention than in secondary prevention. [60]

It is now known that the early risks of subsequent strokes are high, in fact 10% of patients with TIA presenting to an emergency department in the USA had a stroke within 90 days (even with standard treatment). [155] Clearly, patients must be investigated and treatment started as quickly as possible for greatest effect. Patients with TIA or very mild ischaemic strokes can start oral anticoagulants within a day or so, but in patients with larger infarcts anticoagulation should probably be delayed a week or two.

### 2.3.5 Aspirin

The threshold risk of stroke that warrants anticoagulation undergoes intense discussion; those patients whose stroke risk is less than about 2% per year when taking aspirin do not benefit substantially from alternative treatment with oral anticoagulation. [1, 57, 154]

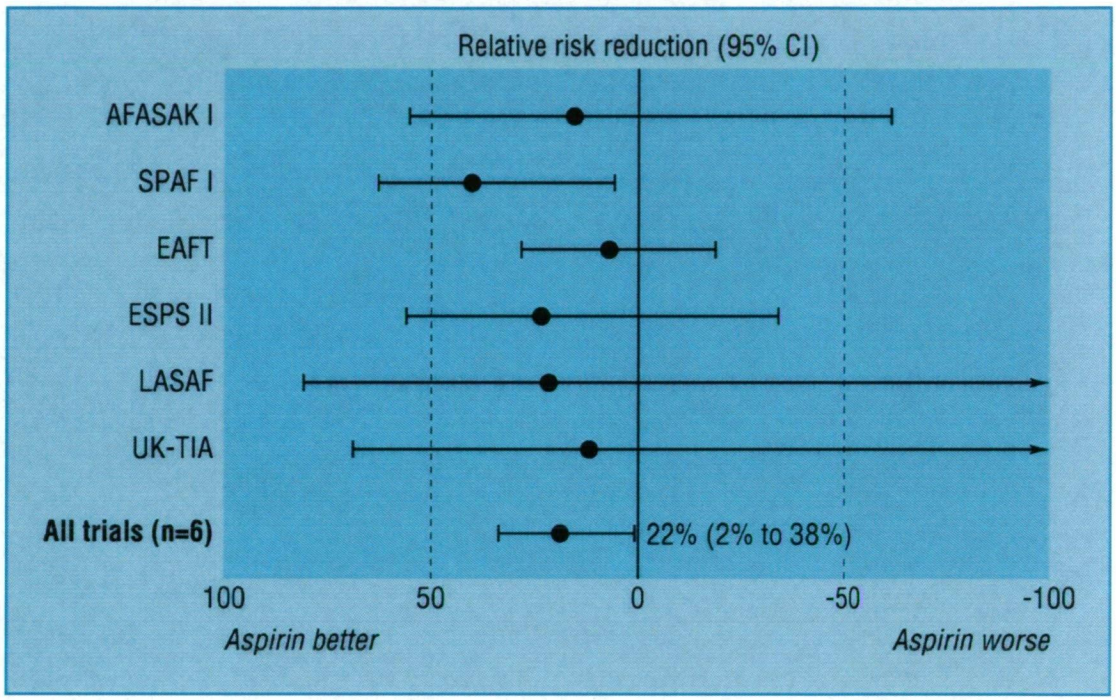



**Figure 13 Antithrombotic therapy for stroke prevention in AF: Aspirin compared with placebo.**
Reproduced from Lip et al. [154]

Aspirin offers only modest protection against stroke for patients with AF compared with warfarin and against placebo as shown in Figure 12 & Figure 13, respectively. Meta-analyses of 5 randomised trials showed a stroke reduction of 19% (95% CI 2% to 34%). [151] The effect of aspirin on stroke in these trials was less consistent than oral anticoagulation. [56, 151] Aspirin reduced stroke occurrence by 33% in primary prevention studies (average stroke rate with placebo was 5%

per year) versus 11% for secondary prevention trials (average stroke rate with placebo was 14% per year). [151]

Aspirin may be more beneficial for reduction of noncardioembolic strokes compared with cardioembolic strokes in AF. [46] Cardioembolic strokes are, on average, more disabling than noncardioembolic strokes. [49] Therefore, because of a greater risk of cardioembolic strokes in AF, less protection is afforded by aspirin.[49] Recent guidelines from the ACC/AHA/ESC suggest the following

> "Aspirin as an alternative in low-risk patients or in those with certain contra-indications to oral anticoagulation" [1]

### 2.3.6 Combination therapy

The SPAF III study compared anticoagulation with a target INR of 2.0 to 3.0 vs anticoagulation targeted at an INR of 1.2 to 1.5 plus aspirin at 325 mg per day. [38] This trial enrolled patients at high risk for ischaemic stroke. The results were dramatic and led to stopping the study early. Those in the low-intensity anticoagulation plus aspirin group experienced a yearly rate of thromboembolism of 7.9% vs 1.9% in the INR 2.0 to 3.0 group, for a RRR of 74%—essentially the same as full anticoagulation vs nothing. An INR of 1.2 to 1.5 provided no protective effect. The SPAF III study also added evidence that aspirin has little efficacy in AF patients at high risk for stroke.

The combination of low-dose oral anticoagulation (INR less than 1.5) with aspirin adds little protection against stroke compared with aspirin alone in patients with AF. [38] Combining aspirin with an oral anticoagulant at higher

anticoagulation intensities may increase the risk of ICH, particularly in elderly patients. [156] Recent guidelines from the ACC/AHA/ESC conclude the following

> "A low dose of aspirin or clopidogrel may be given concurrently with anticoagulation, in patients who have coronary artery disease. These strategies have not been fully evaluated and may have an increased risk of bleeding". [1]

### 2.3.7 Other antiplatelet agents

A single trial compared adjusted-dose warfarin and indobufen, an antiplatelet agent, in patients with AF who had had recent TIA or ischaemic stroke. Fewer strokes occurred among persons who received warfarin than among those who received indobufen (18 compared with 23, respectively). [146]

The addition of dipyridamole to aspirin for patients at high-risk of vascular events (such as those with previous AMI) has not been shown to produce significant additional reductions in serious vascular events. [136] However, one large trial in patients with TIA and ischaemic stroke showed substantial reductions in recurrent stroke, but not in AMI or vascular death. [135] Reasons for part or all of the favourable effect on stroke in that study include the possibility that the newer (and more bioavailable) formulation of dipyridamole was more effective than the older preparation used in earlier trials, that dipyridamole reduced stroke by lowering blood pressure rather than an antiplatelet effect, that the comparative dose of aspirin (25 mg twice daily) was insufficient (i.e., a placebo), and random error (chance). The combination of dipyridamole and aspirin is being tested further in the European and Australian Stroke Prevention In Reversible Ischaemia Trial (ESPRIT).

The combination of clopidogrel and aspirin results in additive benefits against vascular events, with only a modest increase in bleeding, and as stated by Connolly "a trial of combined antiplatelet therapy in AF is warranted". [157] This has lead to the ACTIVE study of 6500 patients which aims to compare clopidogrel plus aspirin against warfarin for stroke prevention in AF

### 2.3.8 Thrombin inhibitors

Ximelagatran is a prodrug of melagatran, an active site-directed thrombin inhibitor. Ximelagatran is well absorbed from the GI tract and undergoes rapid biotransformation to melagatran via 2 intermediate metabolites, H338/57 and H415/04. [158, 159] Ximelagatran has a plasma half-life of 3 to 4 hours and is administered twice daily. The drug produces a predictable anticoagulant response after oral administration, and no coagulation monitoring seems to be necessary. However, melagatran, the active agent, is eliminated via the kidneys, and dose adjustments may be needed in the elderly [160] and in patients with renal insufficiency. One of the side effects of ximelagatran is elevation of liver transaminases, which occurs in approximately 6% of patients. [160] Typically, changes in liver enzymes were asymptomatic and reversible, even if the medication was continued.

The Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) program has been investigating the safety and efficacy of ximelagatran for the prevention of stroke in patients with AF. Promising data from phase II (SPORTIF II) studies that compared ximelagatran with warfarin in patients with NVAF [161] prompted 2 phase III trials. In a randomised, open-label, parallel-group study of approximately 3400 patients (SPORTIF III), fixed-dose

twice-daily ximelagatran was at least as effective at warfarin targeted to an INR of 2.0 to 3.0 in preventing stroke and systemic thromboembolism. Although the combined incidence of major and minor bleeding was significantly lower in those receiving ximelagatran than in those receiving warfarin, there was no statistically significant difference between the 2 groups with respect to major bleeding or ICH.

SPORTIF V enrolled a total of 3922 patients who had NVAF as well as at least one more risk factor; age 75 years or older, prior stroke or systemic embolism, CCF, hypertension or a combination of advanced age and diabetes or coronary artery disease. There were 37 and 51 strokes or systemic embolic events in the warfarin and ximelagatran groups, respectively. This equated to rates of systemic embolic events of 1.2% and 1.6% per year, respectively.

### 2.3.9 Other agents

Elevated homocysteine has been shown to be a risk factor for thrombus formation, [33] and sub-optimal levels of folic acid are associated with high homocysteine levels. It has been shown that homocysteine levels can be reduced by about 25% using a dose of folic acid between 0.5mg and 5mg/day, even in patients who are not vitamin deficient. [162] It remains to be seen whether folic acid should be added to aspirin therapy for patients who have contraindications to anticoagulants

Other agents are being tested for stroke prevention in AF. Idrapinaux is a novel factor-Xa-specific pentasaccharide that is given once a week by subcutaneous injection. Idrapinaux is being compared with warfarin in the AMADEUS study of 5700 patients.

### 2.3.10 Rate control versus rhythm control

Apart from the use of antithrombotic drug therapy to reduce the risk of stroke, [163] there are two main options in managing recurrent or persistent AF: [164]

- ***Rhythm control***, in which treatment is directed toward restoring and maintaining sinus rhythm; and
- ***Rate control***, in which AF is allowed to continue or recur unimpeded, and medications are given to control ventricular rate.

It had widely been accepted and the natural assumption was that rate control (control of the ventricular rate) was inferior to rhythm control (reversion to sinus rhythm). Theoretically, the advantages of maintaining sinus rhythm should include fewer thromboembolic complications, reduced need for anticoagulation and less cardiac failure.

However, antiarrhythmic medications have only modest efficacy for preventing AF recurrences, both symptomatic and asymptomatic, so rate-controlling and anticoagulant drugs must also be used in many patients being treated primarily for rhythm control. Also, antiarrhythmic medications can have serious adverse reactions, including life-threatening proarrhythmia and in the case of the commonly used drug, amiodarone, pulmonary fibrosis, thyroid dysfunction and hepatic toxicity. [165]

Recently published results from one large [61] and two smaller randomised trials, [166, 167] in addition to a previously published study, [168] have shed light on the two treatment strategies. The primary finding in all of the trials was that rate control was not inferior to rhythm control, and that there was some trend towards superiority of rate control.

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial found that 5-year mortality was 21.3% for rate control versus 23.8% for rhythm control ($p = 0.08$). [61] Seventy-one percent of patients had hypertension and 38% had coronary artery disease. The patient populations that were studied were minimally symptomatic and had a mean age of $69 \pm 9$ years, and the findings indicate the benefits of rhythm-control do not, in general, outweigh the risks. [164] Amiodarone was used in 38% of patients being treated for rhythm control initially and in 63% at some time in the trial. Sotalol was used in 31% initially, and by 41% at some time during the trial.

In the RAte Control versus Electrical cardioversion for persistent AF (RACE) study, [167] the primary composite endpoint of cardiovascular mortality, heart failure, thromboembolic complications, bleeding, pacemaker implantation and severe adverse drug reactions occurred in 17.2% assigned to rate control versus 22.6% in the rhythm control arm, which also failed narrowly to reach statistical significance.

The proportion of patients who remained on anticoagulants was 70% in the AFFIRM study and above 86% in the RACE study; doctors were allowed to cease warfarin if sinus rhythm had been present for longer than one month. However, despite this high rate of anticoagulant treatment, rhythm control failed to reduce the rates of stroke or bleeding complications compared to rate control. Of the 80 ischaemic strokes incurred in the AFFIRM trial's rhythm-control arm, 55% occurred after discontinuation of warfarin. A further 21% occurred during warfarin treatment while patients' INR readings were sub-therapeutic (< 2.0). Interestingly, only 31% had AF at the time of their stroke. This finding may be related to episodes of undetected asymptomatic AF, which may keep patients at

continued risk of stroke. A recent study has shown that asymptomatic AF escaped documentation by ECG recordings in 59% of patients and freedom from AF for longer than three months does not preclude subsequent long-lasting AF recurrences. [169]

In the AFFIRM study, patients in the rhythm control group were significantly more likely to be hospitalised and have adverse medication effects than those in the rate control group, which has important cost implications to the health care system. [61] The Pharmacological Intervention in Atrial Fibrillation (PIAF) study showed that relief of symptoms and quality of life measures were similar between rate control and rhythm control groups, but that hospital admissions were more prevalent in the latter. [168]

In sub-group analyses of the AFFIRM trial, rate control had lower risk of death for patients older than 64 years, those without pre-existing CCF, and those with coronary artery disease. A trend in favour of rate control in patients with hypertension in the AFFIRM trial is supported by superiority (primary endpoint 17.3 % v 30.8% for rhythm control) in the corresponding subgroup analysis of the RACE study.

Women had a statistically significant excess of primary end points in the RACE study. Women are prone to more serious side effects associated with antiarrhythmic drugs, since they are at greater risk for excessive drug induced prolongation of the QT interval and torsade de pointes. [170] Female gender, independent of concomitant risk factors may also be a risk factor for stroke among older patients with AF. [37]

None of the presumed benefits of rhythm control were confirmed in the trials. This implies that rate control should be considered a primary approach to

treatment and that rhythm control, if used, should be abandoned early if it is not fully satisfactory. These findings also suggest that it may be unsafe to stop anticoagulation for AF patients treated with a rhythm-control strategy, unless there are no other risk factors for stroke. The populations studied in these trials were representative of the majority of elderly patients with AF. Patients who are elderly (65 years or older) have the highest incidence of AF and this population is increasing in number.

The American College of Physicians has recently endorsed these recommendations for patients with newly detected AF. [171]

> "Rate control with chronic anticoagulation is the recommended strategy for the majority of patients with AF. Rhythm control has not been shown to be superior to rate control (with chronic anticoagulation) in reducing morbidity and mortality, and may be inferior in some patient subgroups to rate control."

Therefore, rate control is safe and should not be considered inferior to rhythm control for minimally symptomatic patients in whom AF is considered likely to recur after cardioversion.

### 2.3.11 Patient preferences and perceptions

The framing of risks, both numerically and linguistically, and the value individuals place on the various gains and losses perceived, have an effect on the choices that they make. This has considerable ethical implications for information providers if manipulation of individuals and populations is to be avoided. [172] Good quality information and graphics are needed to explain risks associated with medical conditions and options—for patients in consultation with their doctors, but increasingly also for members of the public attempting to take responsibility for their own health. [172]

All patients taking warfarin need to understand its risks and the requirements for regular monitoring and accurate dosing. They need to be engaged in the initial decision and in the ongoing process of taking anticoagulants. Many patients view serious strokes as worse than death and would tolerate GI haemorrhages to avoid a stroke. [173] Even after an initial decision is made to take warfarin, there are barriers to smooth anticoagulation. Some patients tire of repeated blood tests, attention to new medications and dietary changes, or minor bleeding and bruising. More substantial bleeding may occur leading to medical visits, diagnostic evaluations, or hospitalisations. These barriers take their toll, with a small proportion of patients ceasing anticoagulant therapy each year.

Patients presented with visual aids depicting the risks and benefits of warfarin therapy elected to take warfarin at a lower level of stroke risk than their physicians preferred to prescribe it. [174] This finding is very important because if patients are more actively involved in the decision making process for stroke prevention it may result in a higher proportion of patients treated with anticoagulants. However, patients need to be educated regarding the implications of AF as a medical condition. In a cohort of patients treated with warfarin for stroke prophylaxis in AF, the majority (61%) of patients' felt that AF was 'not serious', whereas 33% felt it was 'severe' and 6% felt it was a 'very severe' condition. [175]

Although there appears to be incomplete application of trial evidence in real-world practice, the extent of the gap is uncertain since the decision to initiate anticoagulation depends heavily on individual patient preferences and some patients may well decline proven efficacious therapies. [175, 176] In fact, AF is one condition in which active patient involvement in treatment decisions may

substantially impact management, and there is mounting evidence that shared decision making (i.e., patients and clinicians collaborating in devising management plans) for chronic conditions such as AF improves health outcomes. [177]

Despite the desire of many patients to play a more active role in the management of their health, not to mention the evidence that knowledgeable and actively involved patients fare better, patients frequently report difficulties in obtaining information about their condition and its treatment from their health professionals. [178] For example, in an observational study of more than 1000 patient-physician encounters, patients were told the benefits and risks of prescribed therapies less than one-sixth of the time, and only 2% of the encounters included a check that the patient had understood whatever information was offered. [179] Further, there may be concerns about the quality of some information that clinicians do offer. [180] Decision aids have been shown to improve patient knowledge and comfort with their therapies for a variety of conditions, including AF, as well as stimulate their participation in decision making without increasing anxiety. [181]

# PART TWO: IMPROVING ANTITHROMBOTIC USE IN AF

## CHAPTER THREE: INTRODUCTION

## UNDER-UTILISATION OF ANTITHROMBOTICS FOR AF

### 3.1 Burden and cost of stroke in Australia

Stroke is one of the leading causes of death and disability throughout the world. It is the third commonest cause of death in developed countries, exceeded only by coronary artery disease and cancer. [182] About 50% of all ischaemic strokes and TIAs are probably due to atherothrombotic disease of the extracranial or less commonly large intracranial arteries, about 20% arise from emboli from the heart, and about 25% are called lacunar infarcts, probably due to occlusion of one of the small, deep, perforating cerebral arteries; and the remainder are due to much rarer causes (e.g., vasculitis, arterial dissection, Figure 14)

Stroke caused 3% of the world's disability burden in 1990, and by 2020, stroke mortality will have doubled, mainly as a result of an increase in the proportion of older people and the future effects of current smoking patterns in less developed countries. However, stroke attracts far less research funding than heart disease or cancer. [183] About 30% of patients die within a year of a stroke, and of stroke survivors, nearly half are left dependent.

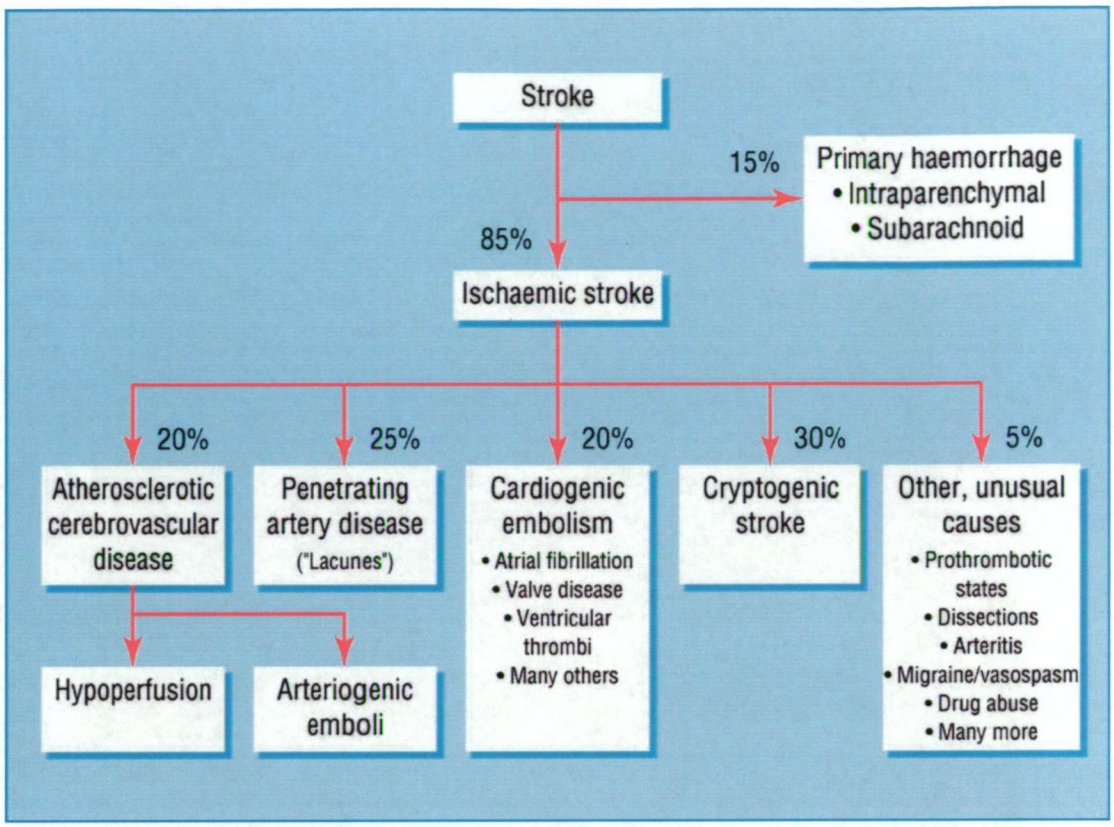



**Figure 14 Classification of stroke by mechanism, with estimates of the frequency of various categories of abnormalities.**
Reproduced from Lip et al. [182]

In Australia the incidence of first in a lifetime ischaemic stroke was estimated to be 22 246 [184] in 1997 and the total costs was estimated at over $A150 million dollars for these events. [185] The total number of strokes first-ever and recurrent in Australia is estimated at about 40,000 per annum. [184, 186] The incidence and costs of strokes indicates that the impact of stroke on the healthcare system is enormous. Any program that aims to reduce the incidence of stroke from any cause has the potential to save the healthcare system a huge amount of money in the short and long-term. [185]

## 3.2 Applying clinical trial results in practice

There have been concerns that the dramatic results from the stroke prevention trials published in the early 1990s might not translate directly to typical clinical practice. Patients enrolled in the trials were highly selected (e.g., <10% of those screened in the SPAF study were enrolled), [140] few very elderly patients participated, and the high quality of anticoagulation management in the trials might not be duplicated in clinical settings. [103]

A number of clinical practice observational studies have indeed found that the risk reduction for stroke in AF afforded by anticoagulants is similar to that reported in clinical trials. [187-189] In a large cohort of patients in clinical practice with AF without contraindications to anticoagulation (11,526 patients) warfarin reduced the risk of ischaemic stroke and peripheral embolism by 51% compared with no warfarin therapy. [189] Anticoagulation was associated with nearly a doubling in the relative rate of ICH, but the additional absolute risk of ICH on anticoagulation was low. [189] As concluded by Go et al. [189] "results of randomised trials of anticoagulation translate well into clinical care for patients with AF".

## 3.3 Under-utilisation of antithrombotics in AF

An early review of studies that assessed under-utilisation of antithrombotics in AF, documented that of those patients with AF whom have no contraindications to warfarin, only 15% to 44% are prescribed warfarin. [174] More recent data is displayed in Table 16 confirming the under-use of antithrombotics in AF

**Reported Rates of Warfarin Use in Patients Without Contraindications***

| Reference | No. of Patients† | Patient Population | Setting | Warfarin Prescribed, No. (%) of Patients |
|---|---|---|---|---|
| Albers et al,[12] 1997 | 171 (60) | AF and stroke, mean age of 75 y | 6 University hospitals in United States | 22 (19.8) |
| Antani et al,[13] 1996 | 98 | AF, mean age of 76 y | 2 Hospitals and 5 general practices in United States | 36 (36.7)‡ |
| Bath et al,[14] 1993 | 95 (20) | AF, aged 32-100 y | Hospital in England | 22 (29.3) |
| Beyth et al,[15] 1996 | 189 | NVAF | United States hospital (n = 104) and office-based visits (n = 85) | (24)‡§ |
| Brass et al,[16] 1997 | 488 (184) | AF, aged ≥65 y; 54% were aged 65-74 y | Medicare patients in United States | 117 (38.4) |
| Gottlieb and Salem-Schatz,[17] 1994 | 238 (40) | AF, mean age of 69 y | HMO patients in hospitals in United States | 156 (78.8) |
| Gurwitz et al,[18] 1997 | 413 | AF, 66% aged ≥85 y | Long-term care facility in United States | 130 (31.5) |
| Hendry et al,[19] 1994 | 131 (52) | NVAF, aged 53-95 y | Geriatric and medical units in Scotland | 12 (15.2) |
| Lip et al,[20] 1997 | 111 | AF, aged 50-105 y | 2 General practices in England | 27 (22.3) |
| Lip et al,[21] 1994 | 170 (49) | AF, aged 38-95 y | General hospital in Scotland | 40 (36.0) |
| Munschauer et al,[22] 1997 | 651 (42) | Chronic AF | 2 Community and 2 tertiary referral hospitals in United States | 232 (38.1) |
| O'Connell and Gray,[23] 1996 | 91 (22) | AF, mean age of 77 y | General practice in England | 14 (24.1) |
| Stafford and Singer,[24] 1996 | 3.1 × $10^6$ Visits | AF, mean age of 70 y | Office-based physician visits in United States | (32.0)§ |
| Sudlow et al,[25] 1998 | 207 | AF, aged ≥65 y | 26 General practices in England | 44 (23)‖ |
| CQIN Investigators,[26] 1998 | 3575 | AF, aged 19-104 y | 12 Canadian hospitals | 852 (23.8) |
| Whittle et al,[27] 1997 | 172 | AF, mean age of 80 y | Medicare beneficiaries at 5 hospitals in United States | 76 (44.1) |

**CQIN indicates Clinical Quality Improvement Network; AF, atrial fibrillation; NVAF, nonvalvular AF; and HMO, health maintenance organization.*
*†Number in parentheses indicates number of patients with contraindications to warfarin.*
*‡Indicates those in whom therapy with warfarin was deemed appropriate by a physician panel.*
*§Exact number of patients not available.*
*‖Data are given as presented in Sudlow et al.[25]*

**Table 16 Studies showing under-utilisation of antithrombotics in AF**
Reproduced from ACC/AHA/ESC guidelines for the management of patients with AF. [1]

The largest clinical practice database of AF and subsequent antithrombotic use is a cohort of ambulatory patients with AF from the Kaiser Permanente Medical Care Program in northern California (the An-Ticoagulation and Risk Factors in Atrial Fibrillation [ATRIA] study cohort). Go and colleagues [190] found that 55% of patients without contraindications received warfarin. In a smaller study, Gottlieb and Salem-Schatz [191] found that nearly 79% of eligible patients in the Harvard Community Health Plan were prescribed long-term warfarin therapy, although this institution was a participant in the large clinical trials, which may explain the high usage of warfarin in this cohort.

A recently published study by Fang et al., [192] examining trends in antithrombotic use from 1991-1992 to 1999-2000, found oral anticoagulant use increased from 28% to 41%, (P = .01 for trend), with the greatest increase in patients aged 80 years and older from 14% to 48%, (P<.001 for trend). Despite this, only 46.5% of patients at high risk for stroke were taking anticoagulants in 1999-2000. As stated by Fang et al. [192] "Although oral anticoagulant use increased, it remains concerning that many patients at high stroke risk are not anticoagulated. As new evidence becomes available on the optimal management of AF, continued monitoring of trends in clinical practice is crucial to help identify areas for quality assessment and practice improvement".

## 3.4 Local data indicating under-utilisation of antithrombotics for AF

A retrospective review of the medical records for consecutive patients who had AF documented on ECG at the major teaching hospital in Tasmania between 1 January 1997 and 30 June 1999 was performed. Most patients were older than 75 years and had at least one condition associated with an increased risk of stroke, risk stratification resulted in most patients (79%) with previously diagnosed chronic or PAF being grouped into the high-risk category. Analysis of the use of antithrombotic drugs in these patients indicated that a large proportion was not taking appropriate therapy. Only 34% of the patients in the high-risk group were taking warfarin (or warfarin plus aspirin) on admission, with 24% taking no antithrombotic at all, as displayed in Table 17. [193]

| Groups | On admission to hospital care<br>Antithrombotics (% of patients) | | | |
|---|---|---|---|---|
| | **Warfarin** | **Aspirin** | **Both** | **None** |
| High risk (n = 359) | 25.1 | 42.3 | 8.9 | 23.7 |
| Medium risk (n = 84) | 31.0 | 41.7 | 7.1 | 20.2 |
| Low risk (n = 13) | 7.7 | 15.4 | 0 | 76.9 |
| Total (n = 456) | 25.7 | 40.6 | 8.3 | 24.6 |
| **Groups** | **On discharge from hospital care**<br>Antithrombotics (% of patients) | | | |
| | **Warfarin** | **Aspirin** | **Both** | **None** |
| High risk (n = 347) | 32.3 | 39.8 | 9.8 | 18.2 |
| Medium risk (n = 77) | 31.2 | 49.4 | 6.5 | 13.0 |
| Low risk (n = 14) | 7.1 | 14.3 | 7.1 | 71.4 |
| Total (n = 438) | 31.3 | 40.6 | 9.1 | 19.0 |

**Table 17 Antithrombotic drug use according to risk of stroke.**
Adapted from Jackson et al. [193]

Patients treated with warfarin were significantly younger, on average, than the non-recipients. For patients in the high-risk category for stroke, the median ages were 75 years and 80 years for recipients and non-recipients, respectively ($P < 0.0001$). This age difference was evident across both genders. All patients aged less than 54 years and at high risk for stroke with no contraindications were receiving warfarin. This steadily declined to 60% of the patients aged 65-74 years, and only 20% of the eligible patients aged greater than 85 years. The use of aspirin was unrelated to patient age and there were no significant gender differences in the use of either aspirin or warfarin.

Thirty-five per cent of all patients (39% of patients in the high-risk category and 24% of the medium-risk category) possessed at least one documented reason for not using warfarin. Of the high-risk patients without any contraindications, 43% and 55% were receiving warfarin (or warfarin plus aspirin) on hospital admission and discharge, respectively. Of the high-risk

patients who were not taking warfarin, 53% had no apparent contraindication to warfarin. For those high-risk patients who had a possible contraindication to warfarin and were not receiving the drug, only 47% had been prescribed aspirin.

## 3.5 Predictors for under-utilisation of antithrombotics for AF

The reasons for the underuse of antithrombotics for stroke prevention are still emerging, but they include physician concern that the benefits of prescribing antithrombotic therapy in clinical trials may not translate into everyday practice. [194-196] This concern may arise because the randomised trials excluded most of the potential participants, with some trials excluding >90% of screened patients. [140, 143, 145] The most common reasons for trial exclusion were advanced age and relative contraindications to anticoagulation.

A study by Gage et al. [197] showed that in univariate analyses, patient age and gender were significantly related to antithrombotic therapy prescription, as was location of the facility at which treatment occurred. Patients aged ≥ 76 years were less likely to receive antithrombotic therapy than were younger patients ($P < 0.001$), females were less likely than males to receive antithrombotic therapy ($P = 0.02$), and patients treated in rural facilities were prescribed antithrombotic therapy less frequently than patients in metropolitan facilities ($P = 0.02$).

In a study by Johnston et al., [198] warfarin users were more likely to be younger and to have conditions predisposing them to ischaemic stroke (hypertension, CCF, and diabetes mellitus). Warfarin users were less likely to have had a prior GI or ICH, conditions predisposing them to falls, alcohol or other drug abuse or dependence, and perceived risk factors for poor compliance. No

significant differences were noted in warfarin use by race or sex. Differences in the prevalence of past TIA or stroke, prior AMI, prior other haemorrhage, liver disease, and renal insufficiency were not significant. In general, patients with more risk factors for stroke were more likely to receive warfarin therapy, while those with more risk factors for haemorrhage were less likely to be treated. [198]

## 3.6 Barriers to prescribing antithrombotics for AF

Enormous evidence-based treatment gaps still exist between knowledge and prescribing practice. For example, even though unequivocal evidence from long-term effectiveness studies shows that control of hypertension reduces morbidity and mortality, only a minority of older adults with hypertension has adequately controlled blood pressures. [199]

These evidence-based gaps are due to patient, physician, and healthcare system factors. Patient factors include poor adherence to complex drug regimens; low tolerance of side effects; and the inability to prioritise long-term health outcomes (including survival) over more immediate issues, such as avoidance of nuisance side effects or competing financial demands. Physician factors include incomplete acceptance of recommended standards of care, competing clinical demands, and barriers to effective communication with patients about the health benefits of adherence. [200] System factors include lack of access to health care, high medication costs, poor longitudinal tracking data on medication use, and complicated formularies.

Several physician surveys have examined the barriers to prescribing anticoagulant therapy. [194-196, 201-205] Review of these studies has also revealed the

same three main categories of barriers to warfarin prescribing: patient-, physician, and healthcare system-related factors. [174]

Patient-related factors such as age, perceived embolic risk and perceived risk of haemorrhage are consistently identified as influencing the decision to prescribe warfarin. [174] Increasing age has consistently been identified as a barrier to anticoagulation. [174] Physicians will also target a lower intensity of INR than recommended in randomised controlled trials for elderly patients. [174]

Few studies have directly questioned physicians regarding their perceived barriers to anticoagulation. The primary factor determining the use of anticoagulants appears to be the weighting of the benefit versus risk in the individual patient. Physicians with good or excellent experiences with warfarin were more likely to prescribe it, but still did not prescribe warfarin for half of their patients. [194] Clinical uncertainty, for example, about the risks and benefits of anticoagulation have not been clearly defined within surveys and the importance of clinical uncertainty remains to be clarified. Clinical uncertainty has ranged from being uncommon, to common enough for physicians to request practice guidelines outlining eligibility for anticoagulant therapy.

The expectation of managing anticoagulation at the level reported in clinical trials requires that health care system services are appropriately planned and resourced. Physicians' fear of haemorrhage likely arises because the risk of haemorrhage doubles in patients prescribed anticoagulants outside of experimental trials. [118, 206] The emphasis on avoiding haemorrhagic strokes and other iatrogenic events may cause physicians and patients to choose therapy that minimises side effects rather than therapy that maximises benefit.

To identify the relative importance of barriers to the prescribing of warfarin, Bungard et al. [174] have suggested a rating scale of barrier importance directly eliciting physician responses. Bungard et al. [180] found that physicians underestimated the RRR with warfarin therapy (mean estimate of 53%) compared with that shown in the RCTs (68%) and overestimated the risk of major haemorrhage (10% absolute annual risk versus 1% respectively). In contrast, the mean RRR of aspirin was estimated to be higher (27%) than that documented in RCTs (21%). [56] Interestingly, family physicians estimated aspirin to be significantly more efficacious and the risk of major haemorrhage with warfarin to be significantly higher than the specialists had estimated. Because warfarin therapy is typically monitored by family physicians, these misperceptions may affect a large absolute number of patients.

The estimation of a higher risk of haemorrhage with warfarin by GPs (compared with specialists) has been reported previously. [195, 196] This may be due to several factors. First, GPs monitor warfarin therapy on a long-term basis and, therefore, they are more likely to witness adverse outcomes in clinical practice. As such, there may be a natural tendency to remember these consequences selectively when the therapeutic benefits are not immediately evident (the avoidance of a thromboembolic event). Second, the higher rates of haemorrhage reported by GPs may reflect the reality of anticoagulant control outside RCTs. Specialists commonly recommend or initiate warfarin therapy based on clinical guidelines and RCTs, or both, but the long-term follow-up is left to the GPs. Patients outside RCTs typically have more concomitant diseases and take more drugs, making it more difficult to provide them with appropriate anticoagulation therapy. What is

needed is further clinician education and strategies to quantify explicitly individual patients' risks and the potential benefits of antithrombotics. [180]

## 3.7 Underuse of preventive medicine

Studies to improve prescribing for older adults are especially important with respect to drug safety, but under-use of potentially effective medications is also a problem. Some drugs are nearly always inappropriate for older adults because safer alternatives are available. [207] Studies have framed the need for better prescribing practices in all settings caring for the elderly. [208] Early studies reported that one in five elderly patients receive an inappropriate drug or dosage. [208] Recent reports suggest that clinicians continue to prescribe potentially harmful drugs. [209, 210] While the prescribing of inappropriate drugs or dosages is a major problem for older adults, some drugs are underused in these patients-for instance, statins for primary prevention of cardiovascular events, [211] and ACE-inhibitors and ß-adrenergic antagonists for cardiovascular disease. [212]

For every patient harmed by lapses in patient safety, more will experience or die from deficient health care and flawed delivery systems, which are problems that a perfect safety record will not take away. People are less likely to die of an overdose of warfarin (a lapse in safety) than of not receiving warfarin at all. The attention that policymakers give to safety should be coupled with a proportionately larger effort to deal with defects in health care that affect more lives. [213]

## 3.8 Aims and objectives: Doctors' beliefs on antithrombotic therapy in AF

This thesis includes two studies examining and modifying the determinants of antithrombotic drug use in AF. The intention of the first study was to learn more about the reasons for the under-utilisation of antithrombotic drugs in clinical practice, by performing a comprehensive survey of Australian doctors investigating the barriers to the prescription of antithrombotic therapy in patients with AF and the relative importance of these barriers. The identification and weighting of these barriers would facilitate the development of programs and educational packages designed to improve the efficacy and safety of antithrombotic drug use in patients with AF.

# CHAPTER FOUR: METHODS

# DOCTORS' BELIEFS ON ANTITHROMBOTIC THERAPY IN AF

## 4.1 Recipients of the survey

The survey was performed Australia-wide. Approximately 10% of all registered GPs and physicians (i.e. specialists in internal medicine, including cardiologists, general physicians, neurologists and geriatricians, but excluding specialists such as gastroenterologists, infectious diseases physicians etc.). A total sample of 2,500 doctors, were randomly selected from the Medical Directory of Australia, 2000 (Australasian Medical Publishing Company Ltd.), which lists details of qualifications and specialty of all registered doctors in Australia. The ratio of selected GPs to physicians was 4:1, to match the Australian ratio.[214] The generation of the random sample was performed by AMPCo Direct, Australasian Medical Publishing Company Ltd.

## 4.2 Conduct of the survey

Those doctors selected were sent a personalised letter containing a letter of explanation about the study (Appendix 1) and the 4-page survey form (Appendix 2). Replies were returned via an enclosed postage paid envelope. A follow-up reminder letter was sent to all the doctors 3 weeks after the initial letter was sent (Appendix 3). A brief preliminary section of the survey form dealt with the demographics of the doctor sample (e.g. years since graduation, gender, qualifications, location of practice - state and whether city/rural, working hours). Also included were questions to ascertain the type and patient demographics of

the practice (e.g. how often the doctor makes therapeutic decisions about patients with AF).

There were 6 case vignettes, hypothetical patients with chronic NVAF, for which the doctors had to indicate what they perceived their risk of ischaemic stroke would be and what treatment they felt would be appropriate. Also, they had to indicate the target INR they would aim for if using warfarin. The correct classification of risk and the recommended therapy were according to the guidelines of Lip, [59] but were also consistent with others. [35, 107, 215, 216]

The major section of the survey form was to seek the doctors' opinions on the appropriate use and barriers to the use of antithrombotic drugs in patients with NVAF. This section predominantly utilised responses on 100 mm visual analogue scales – with extremes marked "no, not at all" and "yes, most definitely". Issues included previous bad experiences with the use of warfarin; perceptions of age of the patient as a barrier to the use of warfarin; GI bleeding, haemorrhage, falls, dementia, alcoholism, liver disease, severe anaemia and poorly controlled hypertension as potential contraindications to the use of warfarin; and views on whether monitoring of anticoagulation is too difficult/inconvenient to arrange.

## 4.3 Statistical analysis

The data of the completed survey were stored and then statistically analysed (Statview® 5.01 for PC/Macintosh computer; SAS Institute Inc., Cary, NC, USA). The median response and its variability were examined for each visual analogue item in the questionnaire, with measurements with a ruler to the nearest integer (in millimetres) for responses to questions with a visual analogue scale. Relationships between some variables (e.g. GP/physician/cardiologist or city/rural

practice versus perceptions of barriers to the use of anticoagulation) were investigated using the appropriate nonparametric statistical procedures (e.g. Spearman rank correlation or Kruskal-Wallis test). For the relationships between the types of doctor versus the responses to the case scenarios, a $\chi^2$ test was used. A p-value below 0.05 was considered statistically significant.

# CHAPTER FIVE: RESULTS

# DOCTORS' BELIEFS ON ANTITHROMBOTIC THERAPY IN AF

## 5.1 Demographics of respondents

Of the 2500 doctors surveyed, 818 (33 %) responded. Seventy-nine were retired or not in practice at the time of the survey and 28 stated that they did not deal with the types of patients in the survey. The 711 relevant responses yielded a 30% response rate. The demographics of respondents are displayed in Table 18.

The respondents were practicing in NSW (33.2%), VIC (24.9%), QLD (17.7%), SA (9.2%), WA (8.8%), TAS (4.1%), ACT (1.8%), NT (0.4%) with no significant difference in state of practice between the different specialties ($p = 0.56$). Most doctors were located in a city (39%) or in a suburban practice (38%). Most of the cardiologists and other specialists were located in the city, 77% and 57% respectively, whereas most of the GPs, 43%, were located in a suburban practice ($p < 0.0001$). In general, the patients seen by physicians were a mix of young and older people (61%). Most of the cardiologists and other specialists had older patients, 73% and 60% respectively, whereas most of the GPs, 70%, were seeing a mix of young and older people ($p < 0.0001$).

| Characteristic | All doctors | GPs | Cardiologists | Other specialists[a] | P value |
|---|---|---|---|---|---|
| **Number**[b] | 711 | 525 | 51 | 132 | |
| Percentage | | (74) | (7) | (19) | |
| **Gender: males** | 508 | 354 | 48 | 106 | |
| Percentage | (72) | (67) | (94) | (80) | $< 0.0001^c$ |
| **Years registered** | | | | | |
| (median and range) | 21 | 21 | 20 | 20 | $0.8^d$ |
| | (1 - 59) | (2 - 59) | (5 - 50) | (1 - 52) | |
| **Location of practice** (Percentage) | | | | | |
| City | 39 | 31 | 77 | 57 | |
| Suburban | 38 | 43 | 22 | 26 | $< 0.0001^c$ |
| Rural | 21 | 24 | 2 | 16 | |
| **Consulting hours/week** | 40 | 40 | 40 | 32.5 | $< 0.05^d$ |
| (median and range) | (0 - 130) | (3 - 130) | (4 - 60) | (0 - 80) | |
| **Patient demographics** (Percentage) | | | | | |
| Young | 10 | 13 | 0 | 3 | |
| Old | 29 | 16 | 73 | 60 | $< 0.0001^c$ |
| Mix of young and old | 61 | 70 | 27 | 37 | |
| **New AF cases/year** | | | | | |
| (median and range) | 5 | 4 | 50 | 22.5 | $< 0.0001^d$ |
| | (0 - 325) | (0 - 100) | (10 - 300) | (0 - 325) | |

[a] Other specialists include physicians, neurologists and geriatricians
[b] Some respondents did not indicate their specialty
[c] $\chi^2$ test
[d] Mann-Whitney test (responses from cardiologist and other specialist combined and compared to GPs)

**Table 18 Characteristics of the responding doctors**

## 5.2 Risk stratification and treatment of case studies

The following case scenarios of patients with AF were used:

(a) 65-year-old male with a history of thromboembolic stroke secondary to AF.
(b) 75-year-old male with a history of thromboembolic stroke secondary to AF.
(c) 76-year-old female with diabetes, hypertension and a previous AMI 10 years ago.
(d) 45-year-old male with hypertension, diabetes, ischaemic heart disease and a past history of TIAs.
(e) 60-year-old female with no contributory risk factors.
(f) 50 year old male with hypertension and ischaemic heart disease and a resolved past history of gastrointestinal bleeding.

The responses to the case scenarios are summarised in Table 19, Table 20 & Table 21. In case scenarios A and B, there was no significant difference between the groups of doctors in risk stratification for the patient, treatment regimen and the chosen INR. It was noteworthy that 14% of the cardiologists indicated a target INR above 3.0 for each case.

There was a significant difference for risk stratification of the patients in scenarios C and D, with the GPs doing better than the cardiologists and other specialists. Only 50% and 71% of all doctors nominated cases C and D as high-risk patients respectively. GPs were more accurate than cardiologists and other specialists at indicating the risk category of stroke for the two cases. An even lower proportion of all doctors recommended that anticoagulants were the treatment of choice (47% and 60% respectively). However, in each case, the cardiologists were more likely to use the recommended therapy, warfarin.

Nearly 80% of all doctors indicated patient E was at low risk of stroke with no difference between the specialties. but a higher proportion of cardiologists

selected warfarin as the appropriate agent for this low-risk individual. Over 40% of all the respondents indicated that they would give no antithrombotic therapy.

The GPs also performed slightly better in categorising patient F according to risk of stroke, with the cardiologists again more likely to initiate anticoagulation. Over one-third of cardiologists and other specialists indicated that this patient was at low risk of stroke. Thirty-six percent of GPs, 20% of other specialists and 16% of cardiologists indicated they would use antithrombotic agents other than aspirin or warfarin, such as clopidogrel, dipyridamole or a combination of these. Twenty percent of all the doctors stated that they would use clopidogrel in this case.

| Case scenario | Correct answer | All doctors (%) | | | GPs (%) | | | Cardiologists (%) | | | Other specialists (%) | | | P value ($\chi^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | High;medium;low | | | High;medium;low | | | High;medium;low | | | High;medium;low | | | |
| A | High | 84 | 15 | 1 | 85 | 14 | 1 | 84 | 16 | 0 | 80 | 20 | 0 | 0.2 |
| B | High | 91 | 8 | 1 | 90 | 9 | 1 | 90 | 8 | 2 | 93 | 6 | 1 | 0.8 |
| C | High | 50 | 45 | 5 | 54 | 42 | 4 | 42 | 50 | 8 | 37 | 53 | 10 | < 0.001 |
| D | High | 71 | 28 | 2 | 75 | 24 | 1 | 51 | 49 | 0 | 62 | 34 | 4 | < 0.001 |
| E | Low | 2 | 20 | 78 | 3 | 20 | 77 | 0 | 29 | 71 | 2 | 14 | 85 | 0.2 |
| F | Medium | 13 | 59 | 28 | 13 | 61 | 25 | 4 | 57 | 39 | 13 | 51 | 35 | < 0.05 |

**Table 19** **Perceived risk of ischaemic stroke for the six different AF patients**

## 5.3 Antithrombotic therapy for case studies

| Case scenario | Correct answer | All doctors (%) | | | GPs (%) | | | Cardiologists (%) | | | Other specialists (%) | | | P value ($\chi^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | War[a]; war/asp[b]; asp | | | War; war/asp; asp | | | War; war/asp; asp | | | War; war/asp; asp | | | |
| A | Warfarin | 91 | 7 | 2 | 90 | 7 | 3 | 90 | 10 | 0 | 95 | 4 | 1 | 0.5 |
| B | Warfarin | 85 | 6 | 6 | 84 | 6 | 7 | 94 | 6 | 0 | 90 | 4 | 6 | 0.6 |
| C | Warfarin | 40 | 7 | 48 | 39 | 6 | 50 | 62 | 14 | 24 | 39 | 6 | 52 | < 0.05 |
| D | Warfarin | 51 | 13 | 26 | 52 | 11 | 27 | 56 | 30 | 8 | 47 | 14 | 28 | < 0.01 |
| E | Aspirin | 20 | 0 | 39 | 20 | 1 | 40 | 36 | 0 | 40 | 11 | 0 | 38 | < 0.05 |
| F[c] | Warfarin or aspirin | 22 | 1 | 24 | 19 | 1 | 20 | 40 | 4 | 34 | 28 | 1 | 35 | < 0.0001 |

[a] warfarin
[b] aspirin and warfarin
[c] 20% of all doctors chose clopidogrel

**Table 20 Treatment selections for the six different AF patients**

| Case scenario | Correct answer | All doctors (%) | | | GPs (%) | | | Cardiologists (%) | | | Other specialists (%) | | | P value ($\chi^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | < 2 ; | 2 – 3 ; | > 3 | < 2 ; | 2 – 3 ; | > 3 | < 2 ; | 2 – 3 ; | > 3 | < 2 ; | 2 – 3 ; | > 3 | |
| A | Between 2-3 | 2 | 91 | 7 | 2 | 91 | 7 | 0 | 86 | 14 | 2 | 92 | 7 | 0.3 |
| B | Between 2-3 | 6 | 87 | 7 | 6 | 87 | 7 | 0 | 86 | 14 | 6 | 89 | 5 | 0.2 |
| C | Between 2-3 | 6 | 89 | 5 | 6 | 89 | 5 | 3 | 89 | 8 | 5 | 91 | 3 | 0.9 |
| D | Between 2-3 | 2 | 89 | 9 | 2 | 89 | 9 | 2 | 86 | 12 | 1 | 91 | 8 | 0.9 |
| E | Between 2-3 | 8 | 88 | 5 | 8 | 89 | 3 | 6 | 89 | 6 | 7 | 79 | 14 | 0.4 |
| F | Between 2-3 | 6 | 91 | 3 | 7 | 91 | 2 | 10 | 90 | 0 | 3 | 88 | 9 | 0.3 |

**Table 21** **Nominated target INR if using warfarin for the six different AF patients**

## 5.4 Doctors' views and knowledge on antithrombotic therapy in AF

The cardiologists were clearly the most accurate when stating the risk of stroke for PAF as compared to chronic AF (Table 22). Less than one-third of all doctors said that the risk of stroke from PAF was the same as for chronic AF. There was a significant difference between the groups of doctors in estimating the stroke risk reduction with warfarin and aspirin. Slightly over one-third of all doctors indicated the risk reduction with warfarin was 66%.

There was a tendency for cardiologists to overestimate the risk reduction with both drugs, while the other specialists and GPs often underestimated the proven benefit of warfarin. Seventy percent of all doctors indicated that the RRR with the use of aspirin was 20%, with other specialists and GPs being most accurate.

The other specialists and GPs also often overestimated the reported risk of major bleeds with warfarin. Forty percent of GPs indicated the risk of major bleeding whilst on warfarin treatment was 5% per year. The cardiologists were clearly the most accurate at estimating major bleeding risk; 88% stated the risk was 1%.

Doctors most likely to state the correct answers for each of (i) the relative risk of stroke from paroxysmal versus chronic AF, (ii) the reduction in risk of stroke with aspirin therapy and (iii) the annual risk of major bleeding in AF patients treated with warfarin were those with the highest numbers of new AF cases per year (Kruskal-Wallis $H = 21.3$, 16.7 and 29.6, respectively, all $p < 0.001$). Performance on these questions was not related to the location of the doctor's practice (city/suburban/rural).

Doctors registered longer were less likely to state the correct answers for each of (i) the relative risk of stroke from paroxysmal versus chronic AF and (ii) the reduction in risk of stroke with aspirin therapy (Kruskal-Wallis H = 11.3 and 12.9, respectively, both $p < 0.01$). Increasing duration of registration as a medical practitioner was also generally related to a poorer performance on classifying patients according to the risk of stroke - this reached statistical significance with cases A, B and E (Kruskal-Wallis H = 6.5, 10.0 and 6.3, respectively, all $p < 0.05$).

The number of new AF cases seen per year by the doctor, location of practice (city/suburban/rural), and the number of hours spent in practice per week were not significantly related to performance on classifying patients according to the risk of stroke. Years registered as a medical practitioner and numbers of new AF cases seen per year were not significantly correlated (Spearman rho = 0.04, $p = 0.3$).

| | All Doctors (%) | GPs (%) | Cardiologists (%) | Other Specialists (%) | P value ($\chi^2$) |
|---|---|---|---|---|---|
| Do you believe that the risk of stroke from paroxysmal AF is: | | | | | |
| less than for chronic AF | 34 | 37 | 30 | 25 | < 0.0001 |
| greater than for chronic AF | 37 | 39 | 10 | 40 | |
| **same as for chronic AF** | 29 | 24 | 60 | 35 | |
| Warfarin reduces the risk of stroke in chronic AF by approximately: | | | | | |
| - 20% | 7 | 7 | 2 | 5 | < 0.01 |
| - 50% | 40 | 41 | 24 | 43 | |
| - **66%** | 38 | 37 | 40 | 40 | |
| - 85% | 15 | 14 | 34 | 12 | |
| Aspirin reduces the risk of stroke in chronic AF by approximately: | | | | | |
| - **20%** | 70 | 68 | 58 | 84 | < 0.001 |
| - 50% | 25 | 26 | 41 | 13 | |
| - 66% | 5 | 6 | 0 | 2 | |
| - 85% | 0 | 0 | 0 | 0 | |
| The annual risk of major bleeding[a] in patients with chronic AF treated with warfarin is approximately: | | | | | |
| - **1%** | 58 | 52 | 88 | 67 | < 0.0001 |
| - 5% | 36 | 40 | 12 | 30 | |
| - 10% | 6 | 7 | 0 | 3 | |
| - 20% | 1 | 1 | 0 | 0 | |

**Table 22 Knowledge of risks of AF and antithrombotic therapy**

[a]e.g. Intracranial or intracerebral haemorrhage, or requiring blood transfusion.
Correct response in bold

## 5.5 Barriers to the prescribing of warfarin

The outcome of the section of the survey form, to seek the doctors' opinions on the appropriate use and barriers to the use of antithrombotic drugs in patients with AF are summarised in Table 23 and Table 24.

A number of factors were perceived by the respondents as being potent barriers to the use of warfarin in patients with AF. Variables with a median response of at least 75 mm on the 100 mm visual analogue scales, in decreasing order of importance, were: active GI bleeding, previous ICH, alcoholism, a history of daily falls, liver disease, severe anaemia, and the concurrent use of NSAIDs. The cardiologists were generally more concerned than GPs about supervised dementia, alcoholism, and a history of falls or poorly controlled hypertension as potential barriers to the use of anticoagulation, but less concerned about a history of resolved GI bleeding or the concurrent use of NSAIDs. While a patient living distant from routine medical care was rated a major barrier to the use of anticoagulation, it was surprising that this was ranked a significantly greater barrier by city and suburban doctors than their rural counterparts (Kruskal-Wallis $H = 12.1$, $p < 0.01$).

The cardiologists and other specialists were generally more likely to agree that there are clear guidelines that can be referred to if unsure of whether to anticoagulate patients with AF, anticoagulation is under-utilised in patients with AF, and most patients with chronic AF would accept treatment with warfarin, and less likely to agree that the risk of haemorrhage with warfarin outweighs the potential benefit for stroke prevention in patients with AF. GPs were more

convinced that the availability of portable INR monitors would assist with the management of patients with AF.

There were several statistically significant, albeit weak, correlations when comparing the number of new AF cases seen per year and years registered as a medical practitioner against potential factors that could act as barriers to the use of anticoagulation. Doctors with the highest numbers of new AF cases per year generally had less concern about bad experiences with prescribing warfarin in the past, advancing age of the patient, prior resolved GI bleeding, and the concurrent use of NSAIDs as potential barriers to the use of anticoagulation, but increased concern about a history of falls or poorly controlled hypertension. Increasing period of registration as a medical practitioner was associated with a slight decline in concern about most of the possible barriers to the use of anticoagulation, particularly active GI bleeding, a history of falls, and liver disease.

As expected, a number of the variables and attitudes were significantly inter-related. For instance, doctors who stated the correct answers for the relative risk of stroke from paroxysmal versus chronic AF, the reduction in risk of stroke with aspirin and warfarin therapy, and the annual risk of major bleeding in AF patients treated with warfarin, were most likely to agree that there are clear guidelines for anticoagulation in AF, anticoagulation is under-utilised in patients with AF, the results given in the large clinical trials can be translated into Australian clinical practice, and most patients with chronic AF would accept treatment with warfarin. Also, these doctors were less likely to agree with the statements that the risk of haemorrhage with warfarin outweighs the potential benefit in stroke prevention in patients with AF, anticoagulation treatment has a

negative impact on quality of life in patients with AF, most patients with AF find the need for close monitoring while receiving treatment with warfarin too inconvenient, or anticoagulation for AF should be initiated in the hospital setting. These respondents tended to be the doctors seeing more new cases of AF each year and, to a lesser extent, doctors who had been registered for longer. Correlation between (i) number of new cases of AF seen per annum and (ii) years registered as a doctor with perceived barriers to anticoagulant use in AF is displayed in Table 25.

| Barrier | All doctors<br>Median (range) | GPs<br>Median (range) | Cardiologists<br>Median (range) | Other specialists<br>Median (range) | P value<br>(Kruskal-Wallis) |
|---|---|---|---|---|---|
| Bad experience prescribing warfarin | 25 (0 - 100) | 25 (0 - 100) | 25 (0 - 85) | 25 (0 - 95) | 0.8 |
| Advancing age of patient | 60 (0 - 100) | 60 (0 - 100) | 60 (0 - 90) | 60 (0 - 100) | 0.9 |
| Active GI bleeding | 95 (0 - 100) | 95 (0 - 100) | 95 (0 - 100) | 95 (5 - 100) | 0.4 |
| Prior resolved GI bleeding | 65 (5 - 100) | 65 (5 - 100) | 55 (10 - 95) | 55 (5 - 95) | < 0.0001 |
| Previous ICH | 90 (0 - 100) | 90 (0 - 100) | 85 (20 - 100) | 85 (15 - 100) | 0.1 |
| Poor control INR | 65 (0 - 100) | 65 (0 - 100) | 65 (0 - 100) | 75 (5 - 100) | < 0.0001 |
| History of daily falls | 75 (0 - 100) | 75 (0 - 100) | 85 (10 - 100) | 90 (25 - 100) | < 0.0001 |
| History of twice-yearly falls | 50 (0 - 100) | 45 (0 - 100) | 55 (5 - 95) | 55 (5 - 95) | < 0.0001 |
| Dementia in an institutionalised setting | 60 (0 - 100) | 55 (0 - 100) | 82.5 (0 - 100) | 65 (0 - 100) | < 0.0001 |
| Alcoholism | 80 (0 - 100) | 75 (0 - 100) | 85 (0 - 95) | 85 (5 - 100) | < 0.001 |
| Liver disease | 75 (0 - 100) | 75 (0 - 100) | 75 (10 - 95) | 75 (0 - 100) | < 0.05 |
| Severe anaemia | 75 (0 - 100) | 72.5 (0 - 100) | 75 (5 - 100) | 75 (0 - 100) | 0.3 |
| Poorly controlled hypertension | 55 (0 - 100) | 50 (0 - 100) | 65 (25 - 95) | 70 (0 - 100) | < 0.0001 |
| Concomitant use of NSAIDs | 75 (0 - 100) | 75 (0 - 100) | 55 (5 - 95) | 75 (0 - 100) | < 0.001 |
| Patient living distant from medical care | 65 (0 - 100) | 65 (0 - 100) | 65 (10-95) | 65 (5 - 100) | 0.6 |

**Table 23 Perceived barriers to anticoagulant use in AF, and differences between groups of doctors.**

The numbers represent median responses (and ranges) on a 100 mm visual analogue scale, where 0 corresponds to "no, not all" and 100 to "yes, most definitely."

| Statement | All doctors<br>Median (range) | GPs<br>Median (range) | Cardiologists<br>Median (range) | Other specialists<br>Median (range) | P value (Kruskal-Wallis) |
|---|---|---|---|---|---|
| Clear guidelines available | 50 (0 - 100) | 45 (0 - 100) | 62.5 (5 - 95) | 67.5 (0 - 100) | < 0.0001 |
| Clinical trials results can be translated into clinical practice | 75 (5 - 100) | 75 (5 - 100) | 75 (5 - 100) | 75 (15 - 100) | 0.08 |
| Patients accept treatment with warfarin | 70 (5 - 100) | 70 (5 - 100) | 72.5 (35 - 100) | 75 (15 - 100) | < 0.01 |
| Anticoagulation should be initiated in hospital | 30 (0 - 100) | 30 (0 - 100) | 25 (0 - 95) | 30 (0 - 100) | 0.3 |
| Anticoagulation is under-utilised | 70 (0 - 100) | 70 (0 - 100) | 75 (5 - 100) | 80 (10 - 100) | < 0.0001 |
| Risk of haemorrhage outweighs potential benefit of warfarin | 25 (0 - 100) | 25 (0 - 100) | 15 (0 - 95) | 20 (0 - 100) | < 0.0001 |
| Anticoagulation treatment has a negative impact on quality of life | 35 (0 - 100) | 35 (0 - 100) | 35 (0 - 90) | 30 (0 - 95) | 0.1 |
| Patients find the need for close monitoring too inconvenient with warfarin treatment | 40 (0 - 100) | 40 (0 - 100) | 40 (0 - 85) | 35 (0 - 85) | 0.2 |
| INR monitors would assist management | 70 (0 - 100) | 75 (0 - 100) | 50 (0 - 95) | 62.5 (0 - 100) | < 0.0001 |

**Table 24 Opinions on anticoagulation in patients with AF, and differences between groups of doctors.**

The numbers represent median responses (and ranges) on a 100 mm visual analogue scale, where 0 corresponds to "no, not all" and 100 to "yes, most definitely".

| Statement | Correlation with AF cases (Spearman rho) | P value | Correlation with years registered (Spearman rho) | P value |
|---|---|---|---|---|
| Bad experience prescribing warfarin | -0.16 | < 0.0001 | -0.04 | 0.3 |
| Advancing age of patient | -0.09 | < 0.05 | -0.08 | 0.05 |
| Active gastrointestinal bleeding | -0.02 | 0.7 | -0.18 | < 0.0001 |
| Prior resolved gastrointestinal bleeding | -0.23 | < 0.0001 | 0.04 | 0.3 |
| Previous ICH | -0.06 | 0.1 | -0.02 | 0.5 |
| Poor control INR | 0.05 | 0.2 | -0.08 | < 0.05 |
| History of daily falls | 0.15 | < 0.0001 | -0.18 | < 0.0001 |
| History of twice-yearly falls | 0.11 | < 0.01 | -0.09 | < 0.05 |
| Dementia in an institutionalised setting | 0.08 | 0.05 | -0.01 | 0.8 |
| Alcoholism | 0.01 | 0.8 | -0.09 | < 0.05 |
| Liver disease | 0.01 | 0.8 | -0.11 | < 0.01 |
| Severe anaemia | -0.01 | 0.9 | -0.06 | 0.1 |
| Poorly controlled hypertension | 0.14 | < 0.001 | -0.08 | < 0.05 |
| Concomitant use of NSAIDs | -0.11 | < 0.01 | 0.01 | 0.8 |
| Patient living distant from medical care | -0.06 | 0.1 | 0.03 | 0.5 |
| Clear guidelines available | 0.16 | < 0.0001 | 0.09 | < 0.05 |
| Clinical trials results can be translated into clinical practice | 0.08 | < 0.05 | 0.12 | < 0.01 |
| Patients accept treatment with warfarin | 0.15 | < 0.0001 | 0.10 | < 0.05 |
| Anticoagulation should be initiated in hospital | -0.11 | < 0.01 | -0.01 | 0.8 |
| Anticoagulation is under-utilised | 0.20 | < 0.0001 | -0.09 | < 0.05 |
| Risk of haemorrhage outweighs potential benefit of warfarin | -0.16 | < 0.0001 | 0.10 | < 0.05 |
| Anticoagulation treatment has a negative impact on quality of life | -0.13 | < 0.001 | -0.04 | 0.3 |
| Patients find the need for close monitoring too inconvenient with warfarin treatment | -0.16 | < 0.0001 | -0.07 | 0.07 |
| INR monitors would assist management | -0.11 | < 0.01 | -0.01 | 0.9 |

**Table 25 Correlation between (i) number of new cases of AF seen per annum and (ii) years registered as a doctor with opinions on anticoagulation in patients with AF**

# CHAPTER SIX: DISCUSSION

## DOCTORS' BELIEFS ON ANTITHROMBOTIC THERAPY IN AF

The intention of this comprehensive survey was to learn more about the reasons for the discrepancy between the clinical trial evidence and prescribing patterns in Australian clinical practice. The response rate of 30% was similar to that achieved in other surveys of doctors' treatment practices [217] and was considered acceptable for this form of research, especially given the relatively long questionnaire. [218]

Overall, the doctors performed well in classifying the case scenarios according to the risk of stroke associated with AF. Perhaps surprisingly, the GPs performed better than the cardiologists and other specialists in estimating the risk of stroke. On the other hand, when it came to the selection of the appropriate drug therapy in these cases, the cardiologists were more likely to nominate the recommended treatment. Possibly because of seeing more patients with AF and being more familiar with the use of warfarin, the cardiologists had a more accurate perception of the potential benefit of warfarin, or even tended to overestimate the benefit, and were less hesitant to recommend its prescription. However, almost half the cardiologists overestimated the reported benefit of aspirin and to a lesser extent, warfarin, in AF. Over one-third of the cardiologists went as far as to give warfarin to a low-risk patient (case E).

Overall, it appears that the cardiologists are more enthusiastic in using antithrombotic therapy. Sometimes, however, this may not always be justified and may pose some risks to the patients. Even though they seemed to have a better understanding of the risk of stroke in patients with AF, GPs were more cautious, tending to overstate the likelihood of bleeding with warfarin and the importance

of some possible contraindications, and to underestimate the benefits of anticoagulation.

The responses to case scenario C were most disturbing, with only half the doctors correctly nominating the patient (a 76 year old female with diabetes, hypertension and a previous AMI) as being at high risk of stroke. This classification and the recommended therapy should have been indisputable according to an array of Australian and international published guidelines. [59, 219-222] In contrast to the other high-risk cases, this patient did not have a history of previous stroke or TIAs, confirming the importance of these as key determinants of the use of anticoagulation in AF. [187, 190, 223, 224] There is apparently under-recognition of other risk factors for stroke in patients with AF, and a greater acceptance of the prescribing of warfarin for the secondary prevention of stroke rather than as a primary prevention approach.

With the exception of one survey [204] all evaluations have used case vignettes, which can have several methodological limitations. [194-196, 201-203, 205] Vignettes attempt, but often are not successful in, mimicking a clinical scenario for the physician. Their use rests on the assumption that responses in hypothetical situations reflect actual clinical practice patterns. Some studies report that physician response to vignettes may not be representative of their clinical practice patterns. [174]

The identification of prescribing barriers is identified indirectly through case vignettes. Assumptions must be made regarding factors triggering the physician's decision. These may be factors in the vignette, however, there may be factors outside of the case that may influence the decision. This information

cannot be captured in this format. Case vignette format does not allow for the assessment of the relative importance of each of the barriers in prescribing.

Responses to case scenario F (a 50 year old male with hypertension and ischaemic heart disease, and a resolved past history of GI bleeding) were also interesting. Almost one-third of all the respondents, and more of the GPs, indicated that they would use antithrombotic agents other than aspirin or warfarin. It would appear that doctors perceive the newer antiplatelet agents, especially clopidogrel, to carry a lower risk of GI bleeding than conventional agents. We are unaware of any published studies of the benefit of clopidogrel in patients with AF, and the case's details fall outside the approved prescribing indications for the drug in Australia (secondary prevention of ischaemic stroke, TIAs, AMI or unstable angina in patients unable to tolerate aspirin or in whom low-dose aspirin therapy was unsuccessful). Only 4% of the patients in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study had NVAF, [225] so its results are not relevant. [59] A Cochrane review concluded that the small absolute benefit of a reduction in GI haemorrhage (0.4% ARR) for clopidogrel compared to aspirin is partially offset by an increased incidence of rash, leading to withdrawal (0.5% absolute risk increase). [139] There is also recent concern about the association between clopidogrel use and thrombotic thrombocytopaenic purpura. [226] Our results would suggest that clopidogrel has been effectively marketed to doctors by the pharmaceutical industry.

The major barriers to the use of warfarin in patients with AF were active GI bleeding, previous ICH, alcoholism, a history of daily falls, liver disease, severe anaemia, and the concurrent use of NSAIDs. These factors would usually constitute clear contraindications to anticoagulation. [220] Some of these factors are

uncommon and it may be that other, more common factors that were ranked slightly lower as barriers to the use of warfarin (e.g. patient living distant from medical care, poor control of INR in the past, or advancing age of the patient) are more important in practice. Some doctors, particularly cardiologists, rated dementia (in an institutionalised setting) as a major barrier to the use of warfarin. While unsupervised dementia is considered a relative contraindication to warfarin, this does not apply to supervised dementia, which has been previously reported as a determinant of non-treatment with warfarin in AF. [227, 228]

Despite the evidence that the elderly patient with AF benefits most from anticoagulation, many doctors still view advancing age of patient as a barrier to the use of warfarin in patients with AF. [144, 187, 196, 201, 224, 227] There are obviously concerns in practice regarding the possibility of poor anticoagulant control and an increased risk of bleeding complications with warfarin therapy in the elderly, an issue that remains in dispute. [144, 216, 229, 230]

The responding doctors generally agreed that the results given in large clinical trials can be translated into Australian clinical practice, anticoagulation is under-utilised in patients with AF, most patients with chronic AF would accept treatment with warfarin, and the availability of portable INR monitors would assist with the management of their patients with AF, while disagreeing that the risk of haemorrhage with warfarin outweighs the potential benefit in stroke prevention in patients with AF. However, the doctors, especially the GPs were not convinced of the availability of clear guidelines that can be referred to if unsure of whether to anticoagulate patients with AF. The lack of clear guidelines was also frequently mentioned in the comments section of the questionnaire.

Several overseas surveys of doctors have been performed to examine the barriers to prescribing anticoagulant therapy. [195, 196, 201, 205] These studies were performed before the publication of the most recent clinical trials. In contrast to our results, one study indicated that cardiologists believed the risk for ischaemic stroke relative to haemorrhage to be lower than did GPs, and therefore cardiologists were less likely to prescribe warfarin. [195] Monette et al. [205] in a study of doctors providing primary care to elderly patients, reported similar key barriers to the use of warfarin in AF as this study: excessive risk of falls, GI bleeding, and previous ICH.

In conclusion, our results indicate scope for improvement in doctors' knowledge about the appropriate use of antithrombotic drug therapy in NVAF and awareness of the results of recent clinical trials. The proven benefit of warfarin was underestimated by almost half the doctors, whereas almost one-third overestimated the benefit of aspirin.

This thesis intended to use the results to design and evaluate an intervention program targeting the identified barriers to the prescribing of warfarin for stroke prevention among suitable candidates. It is evident from the results of this study that some of these potentially important strategies could include the compilation and dissemination of clear guidelines that can be referred to if unsure of whether to anticoagulate patients, focused education on (i) some of the other risk factors, apart from previous stroke or TIAs, in patients with NVAF and (ii) an evidence-based approach to the use of new antiplatelet agents, and trials of portable INR monitors by doctors and selected patients.

# CHAPTER SEVEN: INTRODUCTION

# INFLUENCING PRESCRIBING BEHAVIOUR

## 7.1 Overview

As discussed previously in this thesis, there is increasing recognition of the failure to translate research findings into practice. This has led to greater awareness of the importance of using active dissemination and implementation strategies. Table 26 displays interventions and definitions of these interventions designed to promote the uptake of research findings. An overview of 41 systematic reviews suggests that the most promising approaches are to use a variety of interventions, including audit and feedback, reminders, and educational outreach. [231]

## 7.2 Strategies to improve physician prescribing

Single interventions likely to be effective include educational outreach, opinion leaders, patient-mediated interventions, and reminders. Grimshaw et al. concluded in a systematic review that multifaceted interventions and studies that undertook a "gap analysis" to inform the development of the intervention were more likely to be successful. [231] They also concluded in a review of passive dissemination of consensus recommendations that there was little evidence that passive dissemination alone resulted in provider behaviour change. [231] It concluded that guidelines can change clinical practice and that guidelines were more likely to be effective if they took into account local circumstances, were disseminated by active educational interventions, and were implemented by patient-specific reminders. There was inconclusive evidence about whether guidelines developed

by the end users (e.g., local guidelines) were more likely to be effective than guidelines developed without involvement of the end users (e.g., national guidelines). [231] They concluded that there were no "magic bullets" for provider behaviour change: a range of interventions could lead to provider behaviour change, but no single intervention was always effective for changing behaviour.

Multifaceted interventions combining more than 1 intervention tended to be more effective but might be more expensive. [231] Mailed educational materials alone were generally ineffective, educational outreach approaches and ongoing feedback was generally effective, and there was insufficient evidence to determine the effectiveness of reminder systems and group education. [231] Freemantle and colleagues reviewed 11 studies evaluating the effects of the dissemination of educational materials. [232] None of the studies found statistically significant improvements in practice.

Thomson and associates [233] reviewed the effectiveness of educational outreach visits (academic detailing). Most observed statistical improvements in care (especially when social marketing techniques were used), although the effects were small to moderate. Educational outreach was observed to be more effective than audit and feedback in 1 study, although the cost effectiveness of educational outreach was unclear.

APPENDIX A. TABLE 1. INTERVENTIONS TO PROMOTE PROFESSIONAL BEHAVIORAL CHANGE THAT COULD BE USED TO IMPLEMENT RESEARCH FINDINGS

Educational materials—Distribution of published or printed recommendations for clinical care, including clinical practice guidelines, audio-visual materials, and electronic publications. The materials may have been delivered personally or through personal or mass mailings.

Conferences—Participation of health care providers in conferences, lectures, workshops, or traineeships.

Local Consensus Process—Inclusion of participating providers in discussion to ensure that they agree that the chosen clinical problem is important and the approach to managing the problem (ie, the clinical practice guideline or definition of adequate care) is appropriate. The consensus process might also address the design of an intervention to improve performance.

Educational outreach visits—Use of a trained person who meets with providers in their practice settings to provide information with the intent of changing the provider's performance. The information given may include feedback on the provider's performance.

Local opinion leaders—Use of providers nominated by their colleagues as "educationally influential." The investigators must explicitly state that "the opinion leaders were identified by their colleagues."

Patient-mediated interventions—Any intervention aimed at changing the performance of health care providers where specific information was sought from or given to patients: for instance, direct mailings to patients; patient counselling delivered by someone other than the targeted providers; clinical information collected from patients by others and given to the provider; educational materials given to patients or placed in waiting rooms.

Audit and feedback—Any summary of clinical performance over a specified period of time. Summarized information may include the average number of diagnostic tests ordered, the average cost per test or per patient, the average number of prescriptions written, the proportion of times a desired clinical action was taken, etc. The summary may also include recommendations for clinical care. The information may be given in a written or verbal format.

Reminders (manual or computerized)—Any intervention that prompts the health care provider to perform a patient- or encounter-specific clinical action.

Marketing—Use of personal interviewing, group discussion ("focus groups"), or a survey of targeted providers to identify barriers to change and the subsequent design of an intervention that addresses these barriers.

Multifaceted interventions—Any intervention that includes two or more of the above.

**Table 26 Interventions to promote professional behavioural change that could be used to implement research findings**
Reproduced from Freemantle et al. [232]

Thomson and coworkers reviewed the effectiveness of local opinion leaders. [234] They identified 6 studies; 5 of the 6 trials observed improvements in at least 1 process of care variable, although these results were only statistically and clinically significant in 1 trial. One of 3 trials observed an improvement in patient outcome that was of practical importance. Opinion leaders were observed to be more effective than group audit and feedback in 1 study. They concluded that using local opinion leaders resulted in mixed effects and that further research was required before the widespread use of this intervention could be justified.

Thomson and associates undertook a review of audit and feedback. [235] They identified 13 studies that compared audit and feedback with a no-intervention control group; 8 reported statistically significant changes in favour of

the experimental group in at least 1 major outcome measure, but the effects were small to moderate. The review concluded that "audit and feedback can be effective in improving performance, in particular for prescribing and test ordering, although the effects are small to moderate" and that the "widespread use of audit and feedback" was not supported by the review.

Hunt and colleagues reviewed the effectiveness of computer-based decision support systems. [236] Significant improvements were observed in 9 of 15 drug-dosing studies, 1 of 5 studies on diagnosis, 14 of 19 studies on prevention, 19 of 26 studies on general management of a problem, and 4 of 7 studies on patient outcome. They concluded that computer-based decision support systems might enhance clinical performance for most aspects of care, but not diagnosis. Another review found that different information interventions improved care, including provider prompts, patient prompts, computer-assisted patient education, and computer-assisted treatment planners. [237]

These systematic reviews identified a variety of dissemination and implementation strategies that are effective under certain conditions, but current knowledge is imperfect. Passive dissemination (e.g., mailing educational materials to targeted clinicians) is generally ineffective and is unlikely to result in behaviour change when used alone; however, this approach may be useful for raising awareness of the desired behaviour change. Active approaches are more likely to be effective but are also likely to be more costly. Interventions of variable effectiveness include audit and feedback, and use of local opinion leaders. Generally effective strategies include educational outreach (for prescribing behaviour) and reminders. Multifaceted interventions based on an

assessment of potential barriers to change are more likely to be effective than single interventions.

Publication of new evidence in peer-reviewed journals is associated with modest changes in clinical practice, and these changes may occur soon after the evidence becomes available. [238] Furthermore, adoption of new evidence appears to be accelerated by active promotion. To help narrow the gap between available evidence and best practice, researchers, educators, and policymakers need to move beyond publishing articles and creating practice guidelines. Rather, more active promotional strategies will be needed to accelerate the adoption of new evidence into routine clinical practice.

## 7.3 Aims and objectives: Improving antithrombotic prescribing in AF

The second part of the study modifying antithrombotic drug use in AF described in this thesis was an educational intervention using the process of academic detailing, [239] targeting identified barriers to the use of anticoagulation for stroke prevention in AF, including the compilation and dissemination of clear guidelines. The overall aim was to promote the rational prescribing of antithrombotics for stroke prevention in AF.

# CHAPTER EIGHT: METHODS

# IMPROVING ANTITHROMBOTIC PRESCRIBING IN AF

## 8.1 Guideline development

Guidelines for stroke prevention in AF (Figure 16) were developed from the international [1, 57, 154] and national literature. [60] The guidelines were incorporated into a flow chart and endorsed by the Royal Hobart Hospital (RHH) anticoagulation group. The anticoagulation group consisted of a haematologist, geriatrician, general physicians, cardiologist and clinical pharmacists. Each member of the guideline group would be considered an opinion leader in each of their respective fields. A flow chart design was decided upon to streamline the risk stratification and treatment decisions. The guidelines were incorporated in the 2002 edition of the RHH anticoagulation guidelines (Appendix 4). The Southern Tasmanian Division of General Practice also endorsed the guidelines.

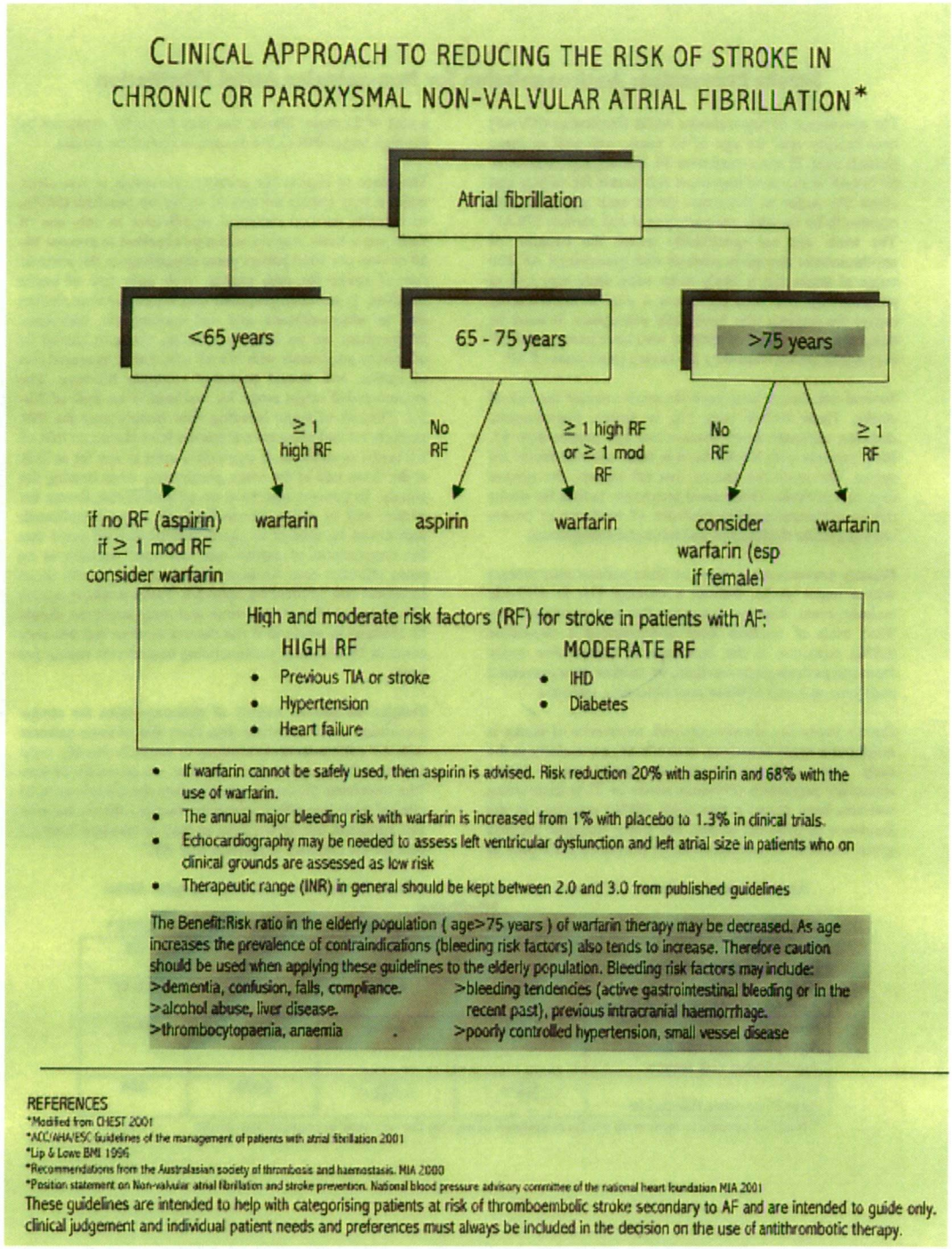



**Figure 16 Guideline flow chart for stroke prevention in AF**

## 8.2 Passive dissemination of the guidelines

The intervention study was conducted in Southern Tasmania (population 230,000), using the remainder, the North of the State (population 245,000) as the control area. The two regions are similar in terms of size, number of GPs, degree

of urbanisation and organisation of quality improvement initiatives. The guidelines, with an explanatory cover letter (Appendix 5), were sent to each GP (n=272) practicing within Southern Tasmania, in early February 2002. The covering letter highlighted local data showing that antithrombotic therapy was being under-utilised. [193]

## 8.3 Process of academic detailing

SLJ contacted each practice to arrange a convenient time to discuss the rationale for prescribing antithrombotic therapy for stroke prevention in AF (May-September 2002). Additional reference material was provided whenever requested. The length and content of each visit varied, depending upon factors such as whether the guidelines had been read, the individual GP's interest, the demographics of the GP's practice and time constraints.

The GPs were supplied with a number of further educational materials. These included a computer mouse pad embossed with the AF guidelines (Figure 17) and the RHH anticoagulation guidelines, which contained a number of items promoting the safe and judicious use of anticoagulants. They were shown a Medical Director (Health Communications Network Ltd. Bundaberg, QLD, Australia) risk stratification computer program (computer-based patient education, an example for a patient 75 years or older with risk factors is given in Appendix 6), which was useful in visually representing to patients their individual risk of stroke.

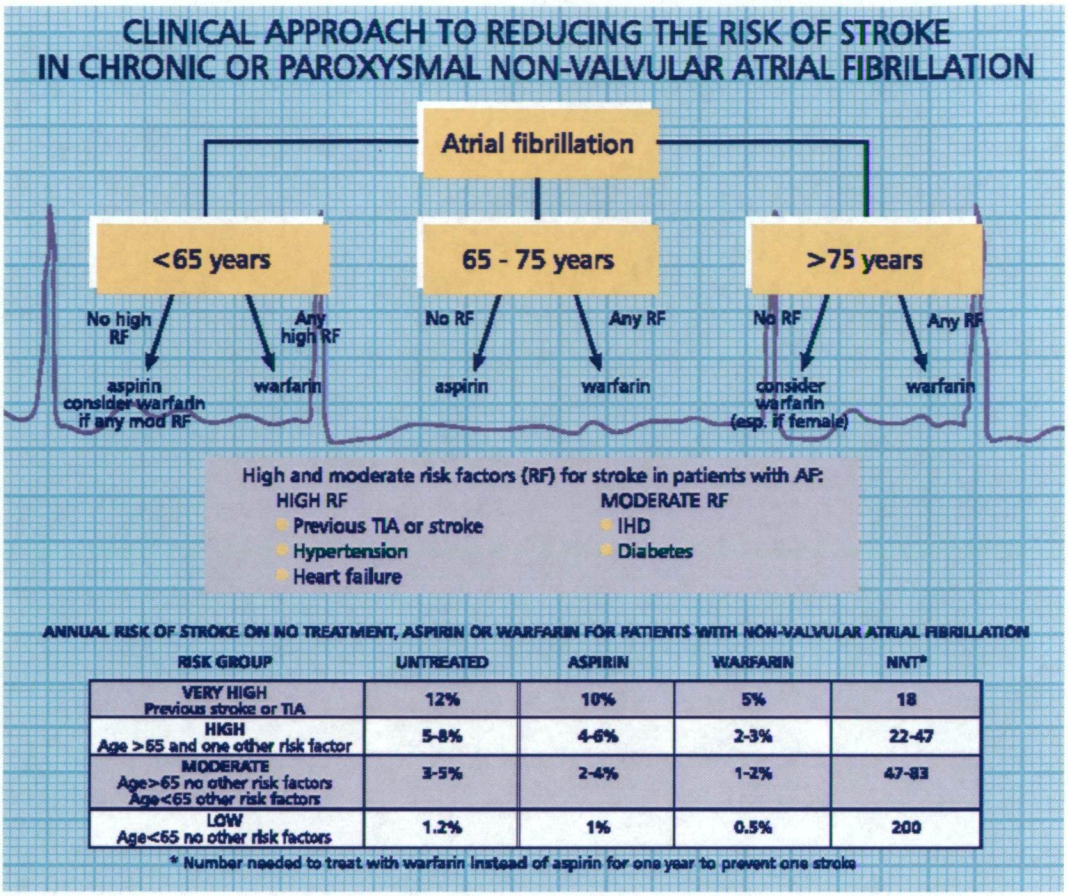



**Figure 17 Computer mousepad embossed with stroke prevention in AF guidelines**

## 8.4 Assessment of effectiveness

### 8.4.1 General practitioner evaluation

Participating GPs were anonymously surveyed (using a visual analogue scale) to assess the usefulness of the mailed information and academic detailing visit. The extremes of the scale were marked (0 not useful or strongly disagree) and (10 useful or strongly agree). The completed evaluation forms were returned via reply-paid envelopes.

### 8.4.2 Pharmaceutical Benefits Scheme data

For comparative purposes, Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS) data were obtained from the Drug Utilisation Sub-committee of the Department of Health & Ageing. Specifically, PBS and RPBS dispensing data for all preparations of warfarin and single preparations of aspirin were obtained for each of the two major regions of Tasmania: South (postcodes 7000-7199) and North (7200-7499), for the periods, 1st February 2001 to 31st January 2002 (pre-intervention) and 1st Feb 2002 to 31st January 2003 (post-intervention). The unit quantities of warfarin dispensed were converted into defined daily doses (DDDs) per 1000 of population; the unit quantities of aspirin were given as number of prescriptions dispensed per 1000 of population.

Changes in the relative prescribing of warfarin and aspirin between and within the control and intervention regions were studied. Statistical comparisons were made between the different areas of the State (i.e. South/intervention region versus north/control region), both before and after intervention, and within each study area (before versus after the intervention) using a normal approximation to the binomial distribution.

### 8.4.3 Admissions to Royal Hobart Hospital

Similar to a previously published study conducted by SLJ, [193] data were collected on patients admitted to the RHH, a 450-bed acute care teaching hospital and the only major public hospital in the southern region (intervention) of Tasmania.

Abstractors who were unaware of the project objectives obtained data retrospectively.

Admission data were analysed for those patients who had a diagnosis of AF or other related conditions as a primary or secondary diagnosis on admission to hospital. Information collected included risk factors for stroke, contraindications to anticoagulation and medications on admission and discharge Patients were categorised according to their risk of stroke using Australian endorsed guidelines. [60] The baseline sample consisted of consecutive patients admitted during the period 1st February 2001 to 31st January 2002. Post-intervention data was for a smaller random sample of patients admitted during the period 1st February 2002 to 31st January 2003, after the educational intervention had commenced. Patients with acute AF, severe valvular disease, who lived out of the region of southern Tasmania or whose medical notes were incomplete were excluded.

The proportions of eligible patients receiving antithrombotics (warfarin and aspirin) in the periods pre- and post-intervention were analysed using $\chi^2$ tests. A p value less than 0.05 were considered statistically significant. The statistical analyses were performed using Statview® 5.01 (Abacus Concepts Inc., Berkeley, CA, USA).

# CHAPTER NINE: RESULTS

# IMPROVING ANTITHROMBOTIC PRESCRIBING IN AF

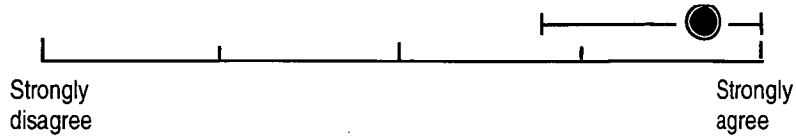
## 9.1 Educational intervention uptake

During the educational intervention, 272 guidelines were originally mailed and subsequently 162 GPs (60% of those in Southern Tasmania) were visited and the guidelines discussed. One hundred and ten GPs were not seen as they did not want the academic detailer to visit (n = 62), were overseas, on maternity leave, de-registered or otherwise unavailable (n = 8) or were 'too busy' to be seen (n = 40). In some of these cases, computer mouse pads, RHH anticoagulation guidelines and SLJ's contact details were left at the general practice (n = 49). The median duration of the educational visits was 15 minutes (range 5-60 minutes), with 40% of GPs seen individually.

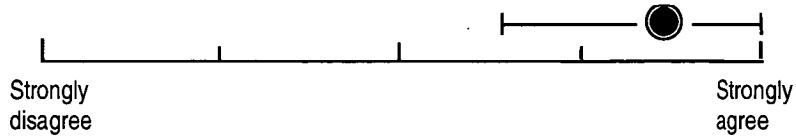
## 9.2 General practitioner survey evaluation

There was an evaluation questionnaire response rate of 76% and the responses are summarised in Figure 18. Unsolicited comments made from visited doctors are displayed in Table 27

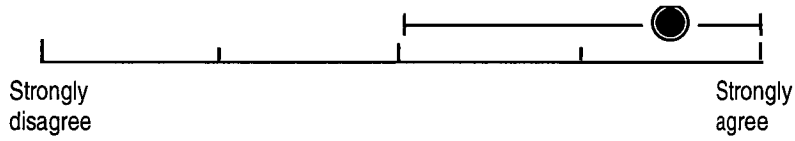
Academic detailing is a good way of receiving up-to-date unbiased information.



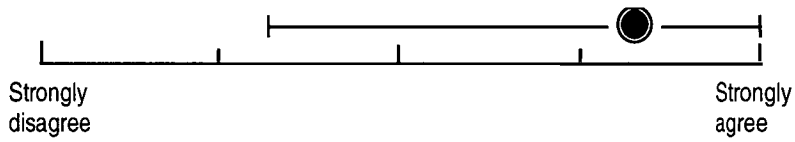

The academic detailing session has reinforced my knowledge about antithrombotic (warfarin or aspirin) therapy for stroke prevention in atrial fibrillation




Prior to the visit by SLJ, I routinely **considered** antithrombotic therapy for stroke prevention in atrial fibrillation




Following the visit, I am now more likely to **consider** antithrombotic therapy for stroke prevention in atrial fibrillation




The RHH anticoagulation guidelines will be useful for general practice

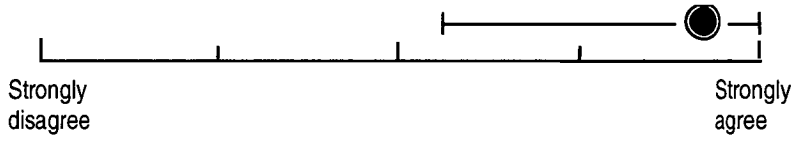



**Figure 18 Median responses to evaluation questionnaire: Improving antithrombotic drug use in AF**
(Ranges are plotted on 10$^{th}$ and 90$^{th}$ percentiles)

| |
|---|
| • Helpful, thank you. |
| • Worthwhile session, thanks. |
| • Easy way to receive up to date info. |
| • These sessions are very useful and helpful. Perhaps provision of a pharmacist's number over any questions may also be worthwhile. Please keep them up. |
| • The session was excellent and there will hopefully be more of them. They are a time efficient way of learning, revising and updating. Also not drug company biased. |
| • Very useful meeting. |
| • I enjoyed Shane's visit. |
| • I was already using the yellow card from the hospital sent by Dr Vial. |
| • Extremely useful and informative. |
| • All patients of mine with AF see a cardiologist. A more useful exercise is the purple book, great. |
| • The major problem with any detailing is time. It needs to be incorporated into our CME prgramme via liaison with the GP Division. |
| • Was very good exercise. |
| • Cardiologists seem to be able to distinguish between chronic and acute AF. |
| • Academic detailing on targeted topics is very effective and enjoyable. Shane is very practical and knows his stuff very good. |
| • Very helpful, thank you |
| • If antithrombotic Rx is initiated in hospital and after hours or weekends, please ensure sufficient supply of medications, as some items are not instantly available at local pharmacy. Almost as important is a letter to say dosage given or requirement I have had several unfortunate incidents. |
| • Very approachable, non-threatening mode of learning as there are no vested interests. This was a good way of getting info and clarifying the mirrors and smoke of drug reps. |
| • Thank you Shane. |
| • Would be useful when the patient is discharged and not began on warfarin, the reason for that decision is clearly delineated, so that the GP knows that it has been seriously considered. |
| • I found this session very helpful and supportive and would appreciate strongly further sessions via the university or division of general practice for provision of unbiased information to balance drug company representative's approach. |
| • Need other information regarding warfarin cessation if needed pre-op and type of operation and dental work. |
| • Thank you, questions answered knowledgeably, useful revision. |
| • Thank you. |
| • Good. |
| • Very useful exercise. |
| • I must admit that I'm not keen on warfarin initiation. Probably not so necessary in an urban setting. |
| • Very useful session, much more efficient use of time compared with drug reps. Please do more topics. |
| • Excellent concise presentation, more please. |

**Table 27 Comments made from visited GPs**

## 9.3 Antithrombotic therapy from patients admitted to the Royal Hobart Hospital

The characteristics of patients admitted to the RHH with AF are displayed in Table 28. There were no significant differences between the two groups (before and after) with regards to key demographic and clinical variables. Table 29 displays antithrombotic therapies for patient groups at baseline and after the intervention. There was a significant increase in the use of warfarin across all patients, those at high risk and patients with chronic AF. There was no significant increase in the use of aspirin.

The use of warfarin on discharge from the hospital reflected the differences between the two groups on admission. Thirty-nine percent of all patients at baseline were discharged on warfarin, compared with 51% post-intervention ($\chi^2 = 5.1$, $p < 0.05$). Forty percent of high-risk patients at baseline were discharged on warfarin compared with 56% post-intervention ($\chi^2 = 7.7$, $p < 0.01$). Of the high-risk patients without contraindications to warfarin, 49% and 64% received warfarin at discharge at baseline and post-intervention, respectively ($\chi^2 = 4.8$, $p < 0.05$).

| | | Baseline (n=245) | Post-Intervention (n=157) |
|---|---|---|---|
| Females (%) | | 50 | 52 |
| Median age (years) | | 75 | 75 |
| Chronic AF (%) | | 51 | 45 |
| Previous stroke (%) | | 14 | 12 |
| Previous TIA (%) | | 10 | 8 |
| Previous stroke/TIA (%) | | 20 | 18 |
| Hypertension (%) | | 64 | 67 |
| Diabetes (%) | | 22 | 25 |
| Ischaemic heart disease (%) | | 42 | 43 |
| Previous AMI (%) | | 23 | 20 |
| Congestive cardiac failure (%) | | 29 | 28 |
| Previous echocardiography (%) | | 69 | 76 |
| Contraindications to warfarin (%) | | 32 | 33 |
| Rhythm control drug therapy (%) | | 26 | 27 |
| Rate control drug therapy (%) | | 54 | 57 |
| Stroke risk [60] | High (%) | 78 | 80 |
| | Medium (%) | 15 | 16 |
| | Low (%) | 7 | 4 |

**Table 28 Hospital patient characteristics before and after the education program**

| | Baseline (n=245) (%) | Post-Intervention (n=157) (%) | P value |
|---|---|---|---|
| Warfarin | 81/245 (33) | 67/157 (43) | 0.05 |
| Aspirin (if not on warfarin) | 103/164 (63) | 54/90 (60) | 0.66 |
| Patients at high risk of stroke | | | |
| Warfarin | 64/192 (33) | 58/125 (46) | 0.02 |
| Aspirin (if not on warfarin) | 85/128 (66) | 47/67 (70) | 0.60 |
| High risk (no C/I* to warfarin) | | | |
| Warfarin | 50/127 (39) | 46/87 (53) | 0.05 |
| Aspirin (if not on warfarin) | 56/77 (73) | 31/41 (76) | 0.74 |
| Patients at intermediate risk | | | |
| Warfarin | 11/37 (30) | 9/25 (36) | 0.60 |
| Aspirin (if not on warfarin) | 15/26 (58) | 7/16 (44) | 0.38 |
| Chronic AF | | | |
| Warfarin | 49/124 (40) | 42/71 (59) | 0.008 |
| Chronic AF at high Risk | | | |
| Warfarin | 38/101 (37) | 35/59 (59) | 0.008 |
| Warfarin (no C/I to warfarin) | 27/66 (41) | 27/41 (66) | 0.01 |
| Paroxysmal AF | | | |
| Warfarin | 32/121 (26) | 25/86 (29) | 0.68 |
| Paroxysmal AF at high Risk | | | |
| Warfarin | 26/91 (29) | 23/66 (35) | 0.40 |
| Warfarin (no C/I to warfarin) | 23/61 (38) | 19/46 (41) | 0.71 |

* C/I = contraindication

**Table 29 Antithrombotic therapies on admission to the RHH at baseline and post-educational intervention**

## 9.4 Antithrombotic prescribing from Pharmaceutical Benefits Scheme data

Dispensing data for antithrombotics in the intervention and control regions of Tasmania are displayed in Table 30. There was a significant increase in the use of

warfarin within the control region, but the increase within the intervention region was greater ($Z = 6.48$, $p < 0.0001$). There was also an increase in the use of aspirin in the intervention region compared with the control region; however the two regions had significantly different usage rates of aspirin prior to the intervention.

| | **Warfarin use (DDDs per 1000 of population)** | | | **Aspirin use (Prescriptions per 1000 of population)** | | |
|---|---|---|---|---|---|---|
| Region | 2001 | 2002 | Statistics | 2001 | 2002 | Statistics |
| Intervention (South) | 1124 | 1191 | $Z = 14.1$, $p < 0.0001$ | 79.0 | 81.1 | $Z = 2.69$, $p = 0.01$ |
| Control (North) | 1127 | 1149 | $Z = 4.83$, $p < 0.0001$ | 88.1 | 88.4 | $Z = 0.28$, $p = 0.79$ |
| Statistics | $Z = 0.95$, $p = 0.34$ | $Z = 8.76$, $p < 0.0001$ | #$Z = 6.48$, $p < 0.0001$ | $Z = 11.49$, $p < 0.0001$ | $Z = 9.03$, $p < 0.0001$ | |

# The increase in the use of warfarin within the intervention region was significantly greater than within the control region

**Table 30 Dispensing of warfarin and aspirin under the PBS and RPBS in Tasmania for the periods pre- and post-intervention**

# CHAPTER TEN: DISCUSSION

## IMPROVING ANTITHROMBOTIC PRESCRIBING IN AF

In this project, educational material and the technique of academic detailing were employed to target the prescribing of antithrombotic therapy for stroke prevention in AF. Success of the educational program was indicated by a significantly greater increase in the prescribing of warfarin in the intervention region and also a significant increase in the use of aspirin compared with the control region. There was also a significant rise in the use of warfarin in a series of patients admitted to hospital with AF, before and after the intervention.

It was apparent that a statistically significant improvement in the prescribing of warfarin occurred in the control region of the state over the course of the study, and this result was not unexpected. The issue of antithrombotics for stroke prevention in AF has received considerable attention and coverage in professional journals over the past few years. It was pleasing that our program was able to achieve significant changes in prescriber behaviour despite this background noise of educational activity. Also, contamination of the two groups of prescribers via professional contact is likely to some extent in any population, particularly a relatively confined one like Tasmania. An improvement in prescribing in the same control region has occurred in a number of previous academic detailing programs conducted in Tasmania. [240-242] The two regions are similar in regards to demographics and treatment practices, and recently, it was shown that the therapeutic management of patients with CCF was very similar between the North and South. [243]

It is evident that there was a clear increase in the use of warfarin following the intervention. From the hospital admission data there was a 10% absolute increase for all patients in the use of warfarin, with higher absolute increases of up to 25% recorded in sub-groups of patients with chronic AF. The likely increases in treatments from educational interventions are generally small, and the effect sizes in this study are consistent with Cochrane reviews. [233]

It was interesting to note the low rates of antithrombotic prescribing for patients with paroxysmal AF - 29% and 35% of high-risk patients in the baseline and post-intervention groups, respectively, were receiving warfarin on admission. This may reflect under-recognition of the link between paroxysmal AF and stroke. A key educational point that was reinforced to GPs was that patients with paroxysmal and chronic AF have a similar risk of stroke. The findings from the AFFIRM [61] study were released after the education program had finished, so the recommendations from this study were not covered during the visits. The findings from AFFIRM and other rate control versus rhythm control trials need to be developed into educational packages and implemented at a general practice level.

This program employed important strategies in relation to guideline dissemination and implementation [244] - the use of guidelines that were well supported by the evidence, with local adaptation through opinion leaders, [245] a "diagnostic analysis" of the target group was implemented prior to the intervention, [246] and a multi-faceted approach with written material, feedback from a local audit of antithrombotic therapy, and an outreach visit was employed.

The use of a simplistic flow chart design to assist in risk stratification was a key change strategy for GPs in applying the evidence of antithrombotics for stroke prevention. Another study utilised an algorithm or flow chart to influence

prescribing with success. [247] This study was conducted in a hospital setting, and increased prescribing of appropriate antithrombotics from 48% before the intervention to 78%, following the intervention.

While academic detailing has been shown to be an effective tool for modifying health professional behaviour, especially prescribing, [233] further research is needed on the specific characteristics that result in practice change. [233] This is the first project to our knowledge that has demonstrated that academic detailing can increase the use of antithrombotics for stroke prevention in patients with AF. However, there clearly is room for further improvement.

The total lifetime cost of ischaemic strokes in Australia was estimated to be Aus$936.8 million (US$709.7 million). [185] It is estimated that AF constitutes 15% [154] of the 40,000 strokes that occur in Australia each year. [184, 186] By increasing the proportion of eligible (approximately 70% of all high risk patients would have no contraindications to anticoagulants) high-risk AF patients treated with anticoagulants, from 39% to 53% as shown in this study, we conservatively estimate that this project has the potential to reduce the number of AF-related strokes by 10% per annum, decreasing the total number of strokes per annum by about 1.5% or 600 strokes if applied across Australia. The reduction in health-care costs associated with stroke would correspond to approximately Aust$14 million per annum. To signify the benefit of this type of intervention, Australia's peak quality use of medicines organisation, the National Prescribing Service (NPS) is conducting detailing visits on antithrombotics in 2004 with a focus on antithrombotics for stroke prevention in AF. [248]

This study did not include a formal economic analysis, although as mentioned under-use of antithrombotics can have a huge impact on the healthcare

system. It is likely that the cost of these types of educational interventions targeting GPs would be small in comparison. There is some evidence that academic detailing can be cost-effective in influencing prescribing behaviour. [249]

There are some limitations to this study. The long-term effects of the intervention are unknown, and key educational messages should be regularly reinforced. In order to assess the effectiveness of the intervention, prescribing data were utilised, which assessed the same time periods of one year (to minimise secular trends biasing data), prior and post-intervention. Our results do not indicate whether patients were receiving warfarin for AF or any other indication, however the use of a control group minimises the risk of bias occurring with this data analysis.

The GPs in the intervention and control groups were not selected randomly, and a controlled before and after study was employed utilising a historical control. It is not known if there were confounders in the geographical areas that may be responsible for the difference in the prescribing of warfarin using the PBS and RPBS data. However, these two areas have been used in previous studies with success [240-242] and, as noted by Eccles [250], it is not appropriate just to consider evaluations only by randomised controlled trial given the complex nature of educational interventions.

The use of before and after data analysis for the hospital cohort of patients may have some limitations in the interpretation of data. It could be suggested that the increase in warfarin use is a secular trend, however, there was little change in the use of antithrombotics for stroke prevention in the same population from 1999 to 2001. In fact, 34% of high-risk patients from the 1999 study [193] were receiving warfarin compared to 33% in 2001. Also, the analysis occurred at the patient

level, while the intervention was applied to GPs. Thus, the analysis did not account for the nesting of patients within physicians, which may lead to artificial inflation of statistical significance.

This educational program significantly improved the prescribing of warfarin for stroke prevention in AF, and if implemented across the spectrum of general practice could significantly reduce the incidence of stroke in patients with AF and its contribution to health-care expenditure.

# PART THREE: PORTABLE INR MONITORS

## CHAPTER ELEVEN: INTRODUCTION

### 11.1 Conventional laboratory or pathology testing

Traditionally, primary care physicians or pathology services manage outpatient anticoagulation. The patient goes to a laboratory (usually a pathology specimen collection centre or general practice in Australia) to have their INR measured, and the result is reported to the physician, who determines the need for dosage adjustments. The need for physician-patient communication can be inconvenient for both parties. The inability to make timely contact with the patient and the potential for misinterpretation of information conveyed by the physician could result in dosage errors.[251]

The method of laboratory INR testing in Australia is by a 5mL venous sample of blood. The blood is drawn to fill a tube containing buffered sodium citrate and centrifuged. The INR is then determined using an analyser with thromboplastin reagent of varying ISI.

### 11.2 Point-of-care testing

There are several types of commercial devices available and manufacturers often do not disclose the way they work. Currently available devices use venous or capillary (fingerprick) blood. Blood flow from the fingerprick, contamination of blood with tissues, haematocrit and platelets are important pre-analytical variables that might affect INR results. In this respect, point-of-care (POC) testing devices are more prone to errors than conventional systems because the fingerprick

method is more difficult to standardise than venepuncture. On the other hand, it should be realised that preanalytical variability may be also high for conventional plasma INR measurement if one considers the effect of different blood collection systems [252, 253] and the time/condition of specimen storage before testing. [254] These variables do not affect POC testing. Table 31 shows the different types of POC testing devices available.

| Instrument | Clot Detection Methodology | Type of Sample | Home Us Approva |
|---|---|---|---|
| Protime Monitor 1000<br>Coumatrak*<br>Ciba Corning 512 Coagulation Monitor*<br>CoaguChek Plus*<br>CoaguChek Pro*<br>CoaguChek Pro/DM* | Clot initiation: Thromboplastin<br>Clot detection: Cessation of blood flow through capillary channel | Capillary WB<br>Venous WB | No |
| CoaguChek<br>CoaguChek S<br>Thrombolytic Assessment System<br>Rapidpoint Coag | Clot initiation: Thromboplastin<br>Clot detection: Cessation of movement of iron particles | Capillary WB<br>Venous WB Plasma | Yes† (CoaguCh only) |
| ProTIME Monitor<br>Hemochron Jr‡<br>GEM PCL‡ | Clot initiation: Thromboplastin<br>Clot detection: Cessation of blood flow through capillary channel | Capillary WB<br>Venous WB | Yes |
| Avosure Pro+§<br>Avosure Pro§<br>Avosure PT§ | Clot initiation: Thromboplastin<br>Clot detection: Thrombin generations detected by fluorescent thrombin probe | Capillary WB<br>Venous WB Plasma | Yes |
| Harmony | Clot initiation: Thromboplastin<br>Clot detection: Cessation of blood flow through capillary channel | Capillary WB<br>Venous WB | Yes |
| INRatio‖ | Clot initiation: Thromboplastin<br>Clot detection: Change in impedance in sample | Capillary WB<br>Venous WB | Yes |

WB indicates whole blood.

*All instruments in this category are based on the original Biotrack model (Protime Monitor 1000) and licensed under differ names. The latest version available is the CoaguChek Pro and Pro/DM (as models evolved, they acquired added capabilities); ear models are no longer available.

†CoaguChek not actively marketed for home use at the time of this writing. Thrombolytic Assessment System not available for hor use.

‡Hemochron Jr and GEM PCL are simplified versions of the ProTIME Monitor.

§Avosure instruments removed from market when manufacturer (Avocet, Inc) ceased operations (2001). Technology has since be purchased by Beckman Coulter.

‖INRange system manufactured by Hemosense, Inc, is currently in development.

**Table 31 Capillary whole blood point-of-care INR instruments.**
Reproduced from Hirsh et al. [73]

## 11.3 CoaguChek S INR monitor

The CoaguChek S concept comprises determination of INR using either capillary or whole venous blood. [253] A number of studies have evaluated the CoaguChek

system that was first introduced in 1993, continuing via the improved CoaguChek PT Test mini test strip in 1998, up to the introduction of the CoaguChek S in early 2000. [253, 255-273]

The CoaguChek INR monitor (Figure 19) is a portable, laser coagulometer that measures the INR using whole blood obtained by fingerprick. [274] The test itself comprises insertion of a test strip into the monitor and the application of a drop of blood onto the test strip. The surface of the test strip is coated with a mixture of iron oxide particles and rabbit brain thromboplastin. The strip is inserted into the monitor and prewarmed to 37°C. A drop of blood (40μL) is then applied to the application field of the test strip where it is drawn by capillary action into the reaction field, where it comes into contact with thromboplastin, triggering the coagulation cascade. Inside the monitor are located two magnets, which cause perpendicular alignment of rod-shaped iron oxide particles found on the test strip. This gives rise to a regular pulsating pattern, which is registered by a photoelectric cell. As the fibrin matrix forms, the movement of iron oxide particles is progressively impeded, before becoming completely impeded. This results in a decrease in reflection that is interpreted by the monitor as the onset of coagulation.


**Figure 19 The CoaguChek S Reflectance Photometer**

The monitor measures the time interval between first contact of the blood sample with thromboplastin and the onset of coagulation and calculates this value as an INR with the aid of a calibration curve. This calibration curve data is stored in a lot-specific code-chip. Cartridges provided by the manufacturer contain several different lots; these lots are standardised by the manufacturer so that the ISI of the cartridges remains constant at 1.70. [256] An INR result is provided within one minute of application of the blood sample to the CoaguChek S monitor. [256]

With the introduction of the CoaguChek S system in early 2000, evaluation studies confirmed that there were no monitor specific influences on test results, no difference in scatter observed between INR values obtained via

CoaguChek and CoaguChek S, and the newer model monitor was rated highly by most study participants. Furthermore, a recent study has confirmed that the CoaguChek S is a suitable alternative to the CoaguChek with comparable accuracy and precision to that of the older system, with a lower amount of technical errors. [257]

## 11.4 Accuracy and reproducibility

The accuracy of the INR measured with POC testing devices depends essentially on the calibration. Presently, the responsibility of calibration rests entirely with manufacturers because access to the software to change encoded parameters is not possible for the majority of commercial devices. Easier calibration procedures for POC testing devices are currently under investigation by the European Concerted Action on Anticoagulation (ECAA) working group. [263-265, 267-270, 272, 275-277]

To check the performance of POC testing, comparing the INRs measured using the devices with those measured using conventional methods is a common method. By definition, the true INR of a given plasma sample should be the one measured with the primary international reference preparation (IRP) for thromboplastin, called 67/40, coupled with the manual (tilt-tube) technique to detect clot formation (defined as the standard method). However, the IRP 67/40 was discontinued many years ago and replaced by other IRPs, which were calibrated against their predecessors. Therefore, the true INR is not known. For practical purposes, it can be assumed that the INR measured with one of the established IRPs for thromboplastin coupled with the manual (tilt-tube) technique is a good approximation of the true value. The INR measured with other conventional systems may also be considered as a good approximation of the true

value only if they have been calibrated against an IRP. The reproducibility assessed for one commercial POC testing device was acceptable (median CV = 4·18%), but poorer than that of the conventional laboratory INR measurement (median CV < 1·5%). [278]

The College of American Pathologists suggests if one method of monitoring anticoagulation is to be replaced or supplemented by another method, the new method should be calibrated against the old method. [279] Therefore, a correlation study of both methods is a crucial step prior to implementing the POC method.

## 11.5 Statistical & clinical agreement

The agreement between paired INR measurements (i.e. those obtained with the POC testing device and those obtained with the standard method) can be assessed by statistically or clinically relevant criteria. Statistically relevant criteria are concerned with the correlation analysis of paired INR measurements and/or comparison of mean values. Although they are widely used it should be realised that these statistical evaluations, if used alone, are not very informative. For instance, two methods might be highly correlated (high correlation coefficient) even though their results are systematically biased. It is more useful to plot the differences of paired measurements against the average value. [280] This enables an assessment of systematic differences over the whole range of measured INRs.

Clinically relevant criteria usually rely on the assumption that the INR values measured for the same patient by two systems are in agreement, if using either INR does not result in changes of dose prescription. Requirements for

agreement of paired INR measurements have been developed [256, 281] and may form the basis for POC testing assessment. Being more closely related to decision making on dose prescription, the agreement based on clinically relevant criteria should be considered more meaningful than that based on statistically relevant criteria.

## 11.6 Clinical endpoints

The reliability of POC testing devices has also been assessed in prospective studies using appropriate end-points i.e. the time in the therapeutic interval and the occurrence of haemorrhagic or thrombotic complications. [282-289] These studies have provided evidence on the reliability of POC testing devices but also on the efficacy of patients self-testing or self-management. A number of studies have been performed on relatively small series of selected patients over the last few years. Generally, all studies found the management with POC testing devices better or at least as effective as the management run by specialists or GPs in combination with conventional laboratory control. Similar conclusions were also reached in those studies in which the comparison of effectiveness has been made versus specialised anticoagulant clinics. [284-286]

## 11.7 Aims and objectives: Royal Hobart Hospital anticoagulation clinic

The objective of the third study in this thesis was to assess the accuracy, reproducibility and clinical agreement of the CoaguChek S portable INR monitor in the Australasian outpatient setting, prior to its evaluation in general medical practice.

# CHAPTER TWELVE: METHODS

# ROYAL HOBART HOSPITAL ANTICOAGULATION CLINIC

## 12.1 Clinic participants

The study was undertaken at the anticoagulation outpatient clinic at the RHH, a 450-bed acute care teaching hospital and the only major public hospital in the southern region of Tasmania, Australia (serving a population of approximately 230,000). This small clinic is conducted weekly and mainly manages patients whose anticoagulant control has been difficult in the community setting. Over a 16-month period, patients who attended the clinic gave informed consent to undergo fingerprick testing with the CoaguChek S INR monitor, in addition to having a normal laboratory INR test. Patients with lupus anticoagulant were excluded, as some of these patients are known to produce errant INR values with phospholipid-based tests. [290]

## 12.2 Pathology methods for determination of INR

Trained nurses drew the venous blood samples by standard techniques into 0.129M (3.8%) sodium citrate tubes. Centrifuged samples were then analysed by the ICA6000 (Sysmex, Japan, distributed by Dade Behring in Australia) within 4 hours of the venepuncture. The thromboplastin reagent used by the laboratory changed from Innovin (Dade Behring) to Recombiplastin (IL) when the Innovin was discontinued in March 2002. The ISI of the Innovin thromboplastin was 1.13, and the Recombiplastin 1.10.

## 12.3 Point-of-care methods for determination of INR

Two operators performed all tests, with basic training in the use of the CoaguChek S monitor. The result from the CoaguChek S was recorded for later comparison with the patient's corresponding laboratory INR value.

## 12.4 Comparison of techniques

Clinical agreement was measured by discrepant INR values and by INR values resulting in a different clinical decision. Discrepant values were defined as INR results from the CoaguChek S that were different from the laboratory in the categorisation of the individual patient's INR value. The INR categories were nominated as 1.0-1.9, 2.0-3.0, 3.1-3.9 and $\geq$ 4.0.

The number of INR values that would have resulted in a different therapeutic decision was based upon clinician decision to leave the warfarin dose the same, or to increase or decrease the dose based upon clinical judgment. This was achieved by giving the attending haematology registrar a list of patients with the two INR readings. The clinician was blinded as to which INR was the CoaguChek S or laboratory value. The clinician indicated whether to maintain the same anticoagulant dose, or to increase or decrease it based on each of the values and the patient's history. The usual therapeutic ranges were 2.0-3.0 for AF and other thromboembolic disorders, and 2.5-3.5 for patients with mechanical heart valves. [132]

Published criteria for clinical agreement (expanded and narrow) [256] were also assessed. Expanded agreement was achieved if comparison between tests fulfilled any of the following: both the CoaguChek S and the laboratory INR were

within, above or below the patient's targeted range, or the difference between the CoaguChek S and the laboratory INR when one of the pair was within the targeted range was no more than 0.5 units. Narrow agreement was achieved if comparison between tests fulfilled any of the following: both the CoaguChek S and the laboratory INR were within the patient's targeted range; both the CoaguChek S and the laboratory INR were above the targeted range and the values were within 0.8 units; both the CoaguChek S and the laboratory INR were below the therapeutic range and the values were within 0.4 units; or the difference between the CoaguChek S and the laboratory INR when one of the pair was within the targeted range was no more than 0.5 units.

## 12.5 Statistical methods

Accuracy of the CoaguChek S was determined by comparing the INRs from the monitor and the laboratory values on a linear regression analysis. A Bland-Altman plot [280] was utilised to assess the magnitude of disagreement between the monitor and the laboratory INRs. A paired t-test ($p < 0.05$ considered significant) was used to compare the INR values with the CoaguChek S and laboratory methods. Reproducibility was defined by the coefficient of variation with three repeated tests done in a random sub-set of clinic patients ($n = 21$).

## 12.6 Interpatient variability

A total of 27 patients had more than five repeated tests over the course of the evaluation. The results were analysed by a number of different measures, these

included correlation coefficient, mean difference, mean percentage difference, category agreement (categories were 1.0-1.9, 2.0-3.0, 3.1-3.9 and >4.0), expanded and narrow agreement, [256] proportion within 10% of laboratory INR and proportion within 0.5 INR units of the laboratory INR. Patients were categorised in the anticoagulation clinic as low agreement if the following variables were satisfied: mean percentage difference was greater than 20% and the mean difference was greater than 0.5 INR units.

Post-hoc analyses of factor levels (F) were assessed in a convenience sample of patients who had low agreement (n=4) and high agreement (n=12). Two patients had died when factor analyses were undertaken and one patient had ceased attending the clinic. Coagulation factors II (FII), VII (FVII) and X (FX) activity expressed in (U/mL) was determined using RecombiPlasTin (Ortho-Clinical Diagnostic Systems, Bucks, UK) using specific factor deficient plasma. Coagulation factor IX (FIX) activity expressed in (U/mL) was determined by an aPTT-based assay (Dade-Behring, Marburg, Germany) using specific factor deficient plasma. Lupus anticoagulant was determined using a dilute Russell viper venom time (DRVVT)-based assay (Gradipore, Australia)

# CHAPTER THIRTEEN: RESULTS

# ROYAL HOBART HOSPITAL ANTICOAGULATION CLINIC

## 13.1 Accuracy & reproducibility

A total of 248-paired samples were obtained from 43 different patients. The mean INR values for the laboratory and CoaguChek S, as well as the status of the anticoagulant control, are listed in Table 32. The CoaguChek S INR values were significantly correlated with the laboratory INR values ($r = 0.90$, $p < 0.0001$; Figure 20). The mean difference in INR (laboratory minus CoaguChek S) was 0.19 (95% confidence interval (CI): 0.14 - 0.25; paired $t = 6.7$, $df = 247$, $p < 0.0001$). The mean coefficient of variation for 21 individual patients with the CoaguChek S INR was 4%, with a range of 0% to 9.1%.

| Parameter | CoaguChek S | | Laboratory |
|---|---|---|---|
| INR (mean ± SD) | 2.44 ± 0.82 | | 2.64 ± 1.03 |
| Mean difference ± SD | | - 0.19 ± 0.46 | |
| Percentage within 0.5 INR units | | 82.5 | |
| Percentage within 10% of laboratory INR | 44.0 | | |
| INR value, n (%) | 248 (100) | | 248 (100) |
| ≤ 1.9 | 69 (27.8) | | 52 (21.0) |
| Mean INR ± SD | 1.67 ± 0.26 | | 1.69 ± 0.26 |
| Mean difference ± SD | | - 0.02 ± 0.23 | |
| Percentage within 0.5 INR units | | 92.2 | |
| Percentage within 10% | | 53.9 | |
| 2.0-3.5 | 155 (62.5) | | 162 (65.3) |
| Mean INR ± SD | 2.51 ± 0.38 | | 2.56 ± 0.43 |
| Mean difference ± SD | | - 0.16 ± 0.37 | |
| Percentage within 0.5 INR units | | 81.1 | |
| Percentage within 10% | | 42.6 | |
| ≥ 3.6 | 24 (9.7) | | 34 (13.7) |
| Mean INR ± SD | 4.25 ± 0.90 | | 4.44 ± 1.48 |
| Mean difference ± SD | | - 0.67 ± 0.70 | |
| Percentage within 0.5 INR units | | 50.0 | |
| Percentage within 10% | | 35.3 | |

**Table 32 Comparison of anticoagulation clinic CoaguChek S and laboratory INR results**

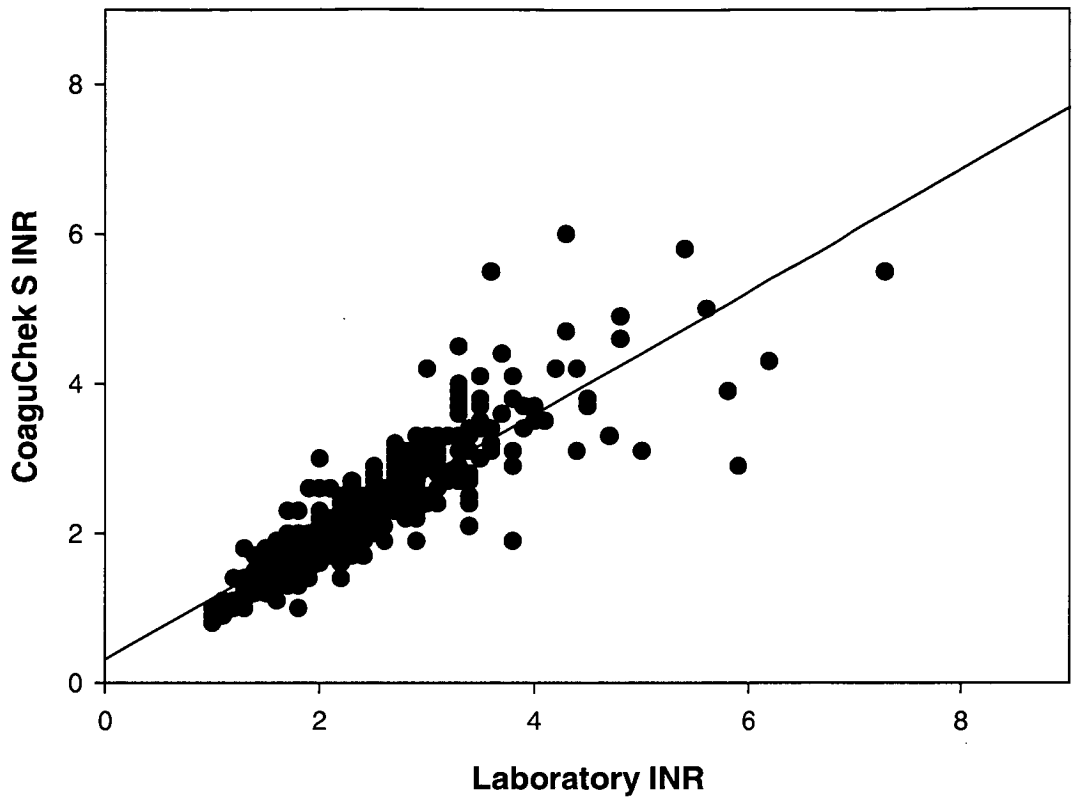



**Figure 20 Relationship between CoaguChek S and laboratory INR values: Anticoagulation clinic**

The Bland-Altman style plot is shown in Figure 21. The CoaguChek S showed only slight variation compared with laboratory testing for INR values < 3.5, with increased scatter around zero as the INR increased to > 3.5. The CoaguChek S was more likely to underestimate the INR, relative to the laboratory, particularly at values > 3.5.

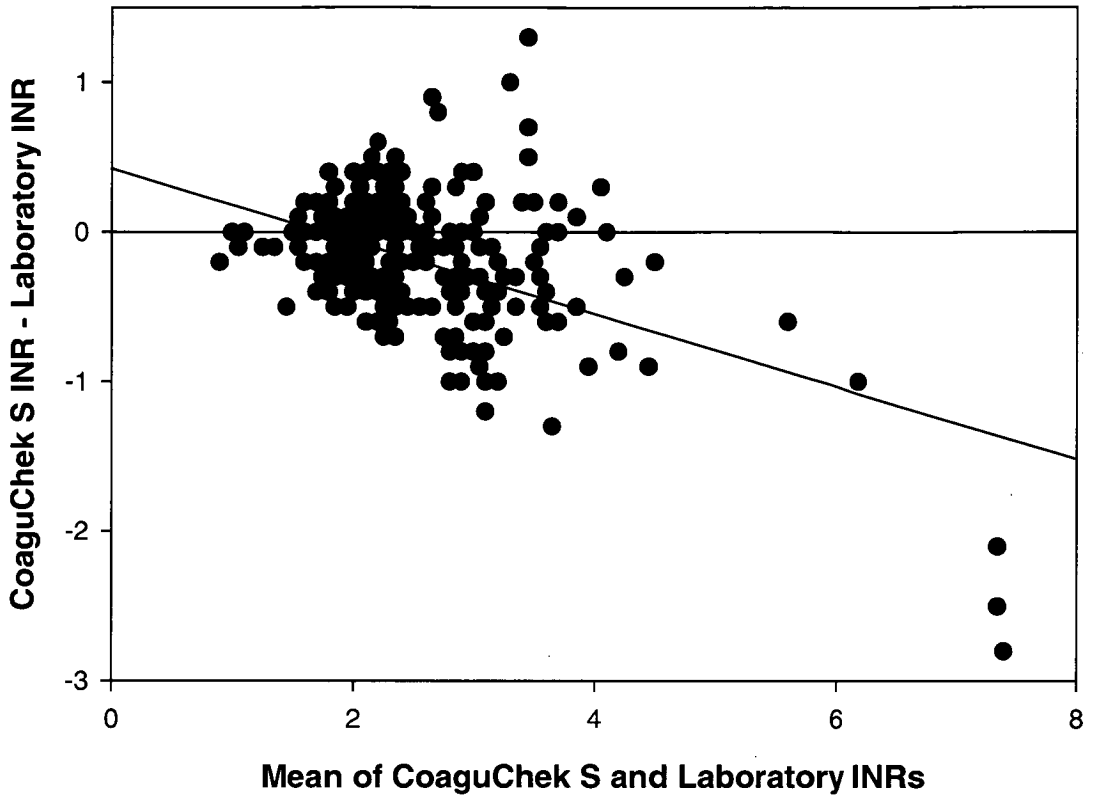



**Figure 21 Bland-Altman plot for CoaguChek S and laboratory INR values: Anticoagulation clinic**

The categorisation of laboratory and CoaguChek S INRs is shown in Table 33. There was a significant relationship between the two methods ($\chi^2 = 261$, df = 9, $p < 0.0001$). Discrepant categorisation of the INR value between the laboratory and CoaguChek S occurred in 31% of the samples. That is, 69% (170/248) of CoaguChek S values were placed in the same nominal category as the laboratory INR. Twenty-four percent were falsely lowered with the CoaguChek S (corresponded to a higher laboratory reading) and 8% were falsely elevated (corresponded to a lower laboratory result).

| | INR Range | CoaguChek S INR | | | |
|---|---|---|---|---|---|
| | | 1.0-1.9 (n = 68) | 2.0-3.0 (n = 135) | 3.1-3.9 (n = 34) | ≥ 4.0 (n = 11) |
| **Laboratory INR** | 1.0-1.9 (n = 51) | 82 | 18 | 0 | 0 |
| | 2.0-3.0 (n = 131) | 20 | 73 | 6 | 1 |
| | 3.1-3.9 (n = 51) | 0 | 53 | 45 | 2 |
| | ≥ 4.0 (n = 15) | 0 | 13 | 27 | 60 |

Values given as percentage of laboratory readings

**Table 33 Comparison of anticoagulation clinic INR categories for CoaguChek S and laboratory results**

## 13.2 Clinical decision making

An analysis of the warfarin dosage decisions of the blinded hematology registrar is shown in Table 34. The relationship between decisions based on the CoaguChek S and those based on laboratory INRs was statistically significant ($\chi^2 = 154$, df = 4, $p < 0.0001$). It can be seen from this table that 73% of all CoaguChek S readings would have prompted the same clinical decision as the corresponding laboratory value - 42% for a decision to decrease anticoagulant dosage based on the laboratory result, 80% for a decision to increase dosage of anticoagulant and 80% for a decision to leave the dose of anticoagulant the same. The mean laboratory INR for dose decreases that were not in agreement was 3.6. Expanded and narrow agreement [256] between the two INR values occurred 90% and 88% of the time, respectively.

| | | CoaguChek S | | |
|---|---|---|---|---|
| | Warfarin dosage decision | Decrease (n = 24) | Same (n = 157) | Increase (n = 67) |
| **Laboratory** | Decrease (n = 45) | 42 | 58 | 0 |
| | Same (n = 152) | 3 | 80 | 17 |
| | Increase (n = 51) | 0 | 20 | 80 |

Values given as percentage of laboratory readings

**Table 34 Analysis of clinician decisions based on CoaguChek S compared with laboratory INR result in the anticoagulation clinic**

## 13.3 Interpatient variability

A total of 27 patients provided more than 5 tests over the trial period amounting to 213 paired INR measurements with a correlation coefficient (r) of 0.9. The individual results are summarised in Table 35. The mean coagulation factor levels for high agreement and low agreement patients are displayed in Table 36. Previous laboratory results did not reveal abnormal haematocrit levels for the patients with poor agreement.

| Patient | Number of tests | R | Mean difference | Mean % difference | Category agreement (%) | Expanded agreement (%) | Narrow agreement (%) | Within 0.5 INR units (%) | Within 10% (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 8 | 0.30 | -0.23 | 10.7 | 100 | 100 | 100 | 100 | 38 |
| 2 | 5 | 0.99 | -0.14 | 5 | 100 | 100 | 100 | 100 | 60 |
| 3 | 5 | 0.91 | -0.14 | 6.6 | 80 | 100 | 100 | 100 | 60 |
| 4 | 9 | 0.62 | -0.14 | 7 | 78 | 100 | 100 | 100 | 56 |
| **5** | **8** | **0.94** | **-0.63** | **29.7** | **25** | **50** | **38** | **50** | **0** |
| 6 | 9 | 0.85 | -0.44 | 20.7 | 56 | 89 | 89 | 78 | 22 |
| 7 | 12 | 0.85 | -0.11 | 3.7 | 92 | 100 | 100 | 92 | 83 |
| 8 | 7 | 0.78 | 0.29 | 10.5 | 57 | 100 | 100 | 72 | 57 |
| 9 | 9 | 0.98 | -0.57 | 13.7 | 67 | 89 | 78 | 78 | 22 |
| **10** | **10** | **0.99** | **-0.59** | **29.4** | **80** | **80** | **60** | **50** | **10** |
| 11 | 11 | 0.91 | -0.15 | 9.1 | 91 | 100 | 100 | 100 | 63 |
| 12 | 5 | 0.99 | -0.26 | 6.9 | 60 | 100 | 100 | 80 | 60 |
| 13 | 10 | 0.83 | -0.15 | 0.4 | 70 | 100 | 100 | 100 | 50 |
| 14 | 11 | 0.27 | -0.02 | 7.3 | 80 | 90 | 90 | 91 | 73 |
| 15 | 8 | 0.91 | -0.33 | 11.1 | 63 | 88 | 75 | 75 | 50 |
| **16** | **11** | **0.96** | **-0.67** | **30.5** | **55** | **64** | **64** | **27** | **0** |
| 17 | 7 | 0.97 | -0.10 | 3.7 | 86 | 100 | 100 | 100 | 85 |
| 18 | 12 | 0.82 | -0.39 | 15.4 | 42 | 92 | 92 | 83 | 25 |
| 19 | 6 | 0.95 | -0.12 | 5.1 | 50 | 100 | 100 | 100 | 50 |
| 20 | 6 | 0.28 | 0.27 | 7.5 | 83 | 83 | 83 | 83 | 50 |
| 21 | 9 | 0.99 | -0.19 | 7.7 | 89 | 89 | 89 | 89 | 67 |
| 22 | 5 | 0.79 | 0.14 | 6.5 | 100 | 100 | 100 | 100 | 60 |
| **23** | **6** | **0.86** | **-0.53** | **27.8** | **17** | **83** | **67** | **33** | **0** |
| 24 | 6 | 0.99 | -0.20 | 4.9 | 100 | 100 | 100 | 83 | 67 |
| 25 | 5 | 0.82 | -0.42 | 15.4 | 40 | 80 | 80 | 80 | 20 |
| 26 | 5 | 0.78 | -0.40 | 1.9 | 60 | 80 | 80 | 80 | 60 |
| 27 | 8 | 0.93 | 0.15 | 6.5 | 63 | 100 | 100 | 88 | 63 |

Patients with low agreement are highlighted

**Table 35 Agreement between CoaguChek S and Laboratory INR for individual patients in the anticoagulation clinic**

| | II | VII | IX | X |
|---|---|---|---|---|
| **High agreement (n=12)** | 0.439 | 0.290 | 0.488 | 0.190 |
| **Low agreement (n=4)** | 0.458 | 0.378 | 0.542 | 0.245 |
| **P value** | 0.86 | 0.32 | 0.50 | 0.40 |

**Table 36 Mean factor levels for poor and high agreement patients in the anticoagulation clinic**

# CHAPTER FOURTEEN: DISCUSSION

## ROYAL HOBART HOSPITAL ANTICOAGULATION CLINIC

When comparing the accuracy of the CoaguChek S to the laboratory method for INR measurement, one problem is the lack of a gold standard for comparison. The true gold standard for the INR value is a test using the manual tilt-tube technique with the use of a WHO IRP thromboplastin. [257] It is important to note that the laboratory analysis is therefore not infallible, and that aberrant results may have been a combination of over or underestimation by the CoaguChek S and vice-versa by the laboratory analysis. For instance, previous studies have found that the variation between portable coagulometers and the laboratory was not larger than the variation encountered between different laboratories measuring a single sample. [278] However, as the comparison to the true gold standard was not available, the laboratory must be treated as the gold standard for the purposes of this evaluation.

In a study designed to test the accuracy of CoaguChek S INR readings compared to laboratory-tested INR values, we found the CoaguChek S to be 90% accurate against expanded agreement criteria and 88% accurate against narrow agreement criteria. [256] This compares favourably with data from other previously published studies where the older model of CoaguChek monitor was found to be 90% accurate against expanded agreement criteria [281] and 86% accurate against narrow agreement criteria. [256] A recent study showed 98% and 97% agreement against expanded and narrow criteria, respectively, with the CoaguChek. [272]

Using the clinician-defined agreement criteria for warfarin dosing, the CoaguChek S was found to be accurate 73% of the time for all decisions. It is

important to note that a decision to increase the anticoagulant dose based on the CoaguChek S value never resulted in a clinical decision to decrease the anticoagulant dose based on the laboratory value. Similarly, the clinician would not have decreased the anticoagulant dose based on the CoaguChek S when they actually increased the dose based on the laboratory value.

The CoaguChek S performed well for dose increases and when no change was made to therapy, however it performed less adequately when dose decreases were compared. It would appear that the CoaguChek S generally gives an adequate indication of high INRs if they are above 3.5. If dose decreases are made on the cusp of the therapeutic range the monitor performs less consistently in clinical terms. The definition of agreement used in this analysis was based on the clinician decision to maintain, lower, or increase the dose of anticoagulant, based on each of the paired samples, and took into account factors such as prior INR values, patient factors and trends in INR. This method of comparison is more relevant to actual practice than the arbitrary expanded and narrow agreement criteria used in prior evaluations.

In a recent study analysing the CoaguChek S, [257] agreement was found 75.5% of the time. The agreement criteria in this case were stricter than any previously used in the literature. The criteria for discrepancy was defined as 1 INR outside of the therapeutic range and the other value within the range, or both INR values outside of the therapeutic range and differing by $\geq 0.5$ INR units.

The CoaguChek S produced reproducible INR results, with a mean coefficient of variation below 5%. This study found that the CoaguChek S had a similar correlation ($r = 0.90$) with laboratory INRs as those seen in prior studies of the CoaguChek and the CoaguChek S ($r = 0.91$-$0.97$). [291] Regression analysis is

only a measure of correlation, not accuracy; a far superior measure is the Bland-Altman analysis. [280] Both of these analyses indicated a general underestimation of the INR, which may need to be factored in to the interpretation of INR results given by the CoaguChek S monitor. Eighty-three percent of all dual measurements were within 0.5 INR units in this study, which compares favourably to the figure of 79% reported by Douketis et al. [256]

As with prior evaluations, the CoaguChek S was most accurate when within the bounds of therapeutic INRs. This finding has also been observed with other portable INR monitors. [274, 278, 292] The proportion of dual INR measurements within 0.5 INR units for laboratory INR ranges of <2.0, 2.0-3.0, 3.1-4.0 and >4.0 was found by Douketis et al. to be 98%, 87%, 57% and 21%, respectively. These data closely match our data for similar ranges of <1.9, 2.0-3.5 and ≥ 3.5, giving values of 92%, 81% and 50%, respectively, within 0.5 INR units. [256] They concluded from the results of their study that the CoaguChek monitor "achieved a clinically acceptable level of accuracy when compared to the traditional laboratory method and provides a suitable alternative method of monitoring the INR in patients receiving warfarin". [273] It has also been noted "as with any method of measuring the INR, if a high value is found that is not consistent with what was expected, a repeat test with an alternative method may be considered".[257]

This and most other studies have shown that the CoaguChek and CoaguChek S devices produce INR values that are highly correlated with laboratory INR values (r = 0.91 - 0.97) and agree with the laboratory INR in therapeutic decisions or dosage alterations in 81-92% of cases. [256, 259, 278, 291, 293, 294] A recent study by Reiss et al. [295] has been the only study that has found that the CoaguChek system

showed relatively poor agreement with the laboratory method. The findings of this study were that mean differences in paired INR values were small, but 95% CIs were wide (-1.08 to 1.36), and the correlation coefficient (r) was found to be 0.72.

The anticoagulation clinic utilised in this study is used by GPs for patients with poor control of their INR. Four of the patients with multiple testing had low agreement compared to conventional laboratory INR. There may be an underlying or idiopathic reason that causes these patients to be unstable with their INRs and subsequently give lower correlated readings with the CoaguChek S monitor. Variation between laboratories has been observed in previous studies, [278, 296] and theories such as the insensitivity of thromboplastins used have been proposed as reasons for this. [278, 297]

Recently, Atterman [298] has proposed that the validity of predicted INR is affected by two components; a systematic error in the slope estimate and the interaction between patients and PT systems. Previous studies have noted that individual sample differences exist when stored samples have been tested. [299] There are a number of pre-analytical variables that can affect the accuracy of the POC coagulation monitors, these include squeezing of the finger and the temperature of the patients' fingers.

Factor VII dysfunction has been reported to adversely affect the accuracy of rabbit brain thromboplastin tests [300] while not adversely affecting bovine or human thromboplastins. Although there was no significant difference between the factor levels for patients with high and low agreement, the patient numbers were small and statistical power is low. This is the first evaluation that has reported individual patient accuracy with the use of the CoaguChek S monitor; further

studies are needed to identify patients with low agreement and reasons behind this phenomenon.

# CHAPTER FIFTEEN: METHODS

# RURAL GENERAL PRACTICE INR MONITORING

## 15.1 Rural general practice INR monitoring

This project aimed to evaluate the usefulness and accuracy of portable INR monitors in Australian rural medical practice.

## 15.2 General practices and training methods

The CoaguChek S monitor was evaluated in 15 rural medical practices: in Tasmania (8), South Australia (4) and Northern Queensland (3). The rural practices were identified by liaison with University Departments of Rural Health (UDRH) in each state. Once identified, SLJ and another researcher traveled to each site to educate the GPs and/or practice nurses on the accurate and effective use of the monitor. They were given a laminated A4 sheet (Appendix 7) outlining the use of the monitor and a list of common problems and their management. They were instructed to obtain written informed consent to undertake testing on patients (Appendix 8). All sites received the same training with the CoaguChek S and all had access to further assistance from investigators if required. A monitor was left at each practice for approximately 2 to 3 months.

## 15.3 Methods for laboratory and point-of-care determination of INR

The laboratory procedure for INR determination varied between the general practice sites, and as such was not uniform for the entire analysis. Patients taking warfarin at these practices were asked to provide a fingerprick sample of blood for the CoaguChek S at the same time, as they were to have a venous sample taken for normal laboratory measurement of INR. The results were tabulated on an individual patient form (Appendix 9) and compared once the pathology result was obtained. The GPs or practice nurses also completed a series of questions for each patient.

## 15.4 Evaluations

A questionnaire was supplied to each practice and completed at the end of the trial period by the primary user of the CoaguChek S monitor. Responses were assessed quantitatively via a visual analogue scale with the aim of evaluating the user's overall experience with the monitor. The extremes of the 10-cm scales were marked with (0) "No, not at all" and (10) "Yes, most definitely".

## 15.5 Statistical methods

The INR values from CoaguChek S and the laboratory were compared using regression analysis. A Bland-Altman plot [280] was utilised to assess the magnitude of disagreement between the CoaguChek S and the laboratory. The accuracy of the CoaguChek S at INR values $\leq$ 1.9, between 2.0-3.5 and $\geq$ 3.6 was also

evaluated. Examined in these categories was the mean difference of the INR value, the magnitude of the INR difference, the proportion of INR measurements within 10% [268] and the proportion of dual measurements that were within 0.5 INR units. Published criteria for clinical agreement; (expanded and narrow) [256] were also assessed, as in the anticoagulation clinic.

# CHAPTER SIXTEEN: RESULTS

# RURAL GENERAL PRACTICE INR MONITORING

## 16.1 Descriptive analysis

In total, 401-paired samples were measured from 169 anticoagulated patients from the 15 rural general practices that completed the evaluation. Table 37 shows the number of patients and INR readings from each site, as well as the correlation coefficient between laboratory and CoaguChek S INR values for each site.

| Practice & location | INR values n (% of total) | Patients n (% of total) | r |
|---|---|---|---|
| 1 Nthn Qld | 19 (4.7) | 7 (4.1) | 0.92 |
| 2 Nthn Qld | 54 (13.5) | 30 (17.8) | 0.84 |
| 3 Nthn Qld | 50 (12.5) | 13 (7.7) | 0.91 |
| 4 Tas | 61 (15.2) | 19 (11.2) | 0.91 |
| 5 Tas | 15 (3.7) | 10 (5.9) | 0.98 |
| 6 Tas | 43 (10.7) | 16 (9.5) | 0.93 |
| 7 Tas | 18 (4.5) | 9 (5.3) | 0.86 |
| 8 Tas | 13 (3.2) | 6 (3.6) | 0.96 |
| 9 Tas | 3 (0.7) | 2 (1.2) | 0.99 |
| 10 Tas | 35 (8.7) | 12 (7.1) | 0.92 |
| 11 Tas | 34 (8.5) | 12 (7.1) | 0.93 |
| 12 Sth Aust | 11 (2.7) | 3 (1.8) | 1.00 |
| 13 Sth Aust | 21 (5.2) | 21 (12.4) | 0.85 |
| 14 Sth Aust | 16 (4.0) | 6 (3.6) | 0.92 |
| 15 Sth Aust | 8 (2.0) | 3 (1.8) | 0.94 |

**Table 37 Individual general practice results**

## 16.2 Accuracy and clinical agreement

Figure 22 and Figure 23 show conventional regression analysis of CoaguChek S versus laboratory results and a Bland-Altman plot, respectively. The CoaguChek S INR values were significantly correlated with the laboratory INR values ($r = 0.89$, $p < 0.0001$). The CoaguChek S showed slight variation compared with laboratory testing for INR values <3.5, with increased scatter around zero as the INR increased to >3.5. This finding suggests that the system was more likely to underestimate the INR value, relative to the laboratory, particularly at values >3.5.

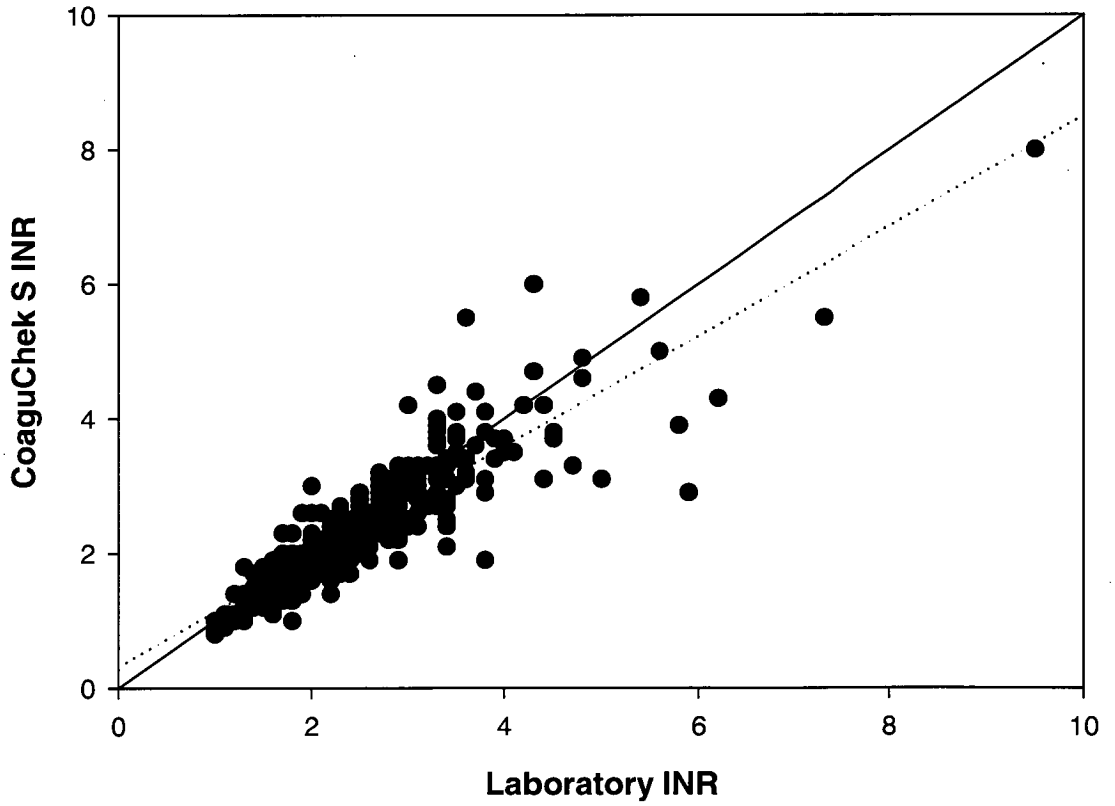



**Figure 22 Relationship between CoaguChek S and laboratory INR values: General practice INR monitoring**

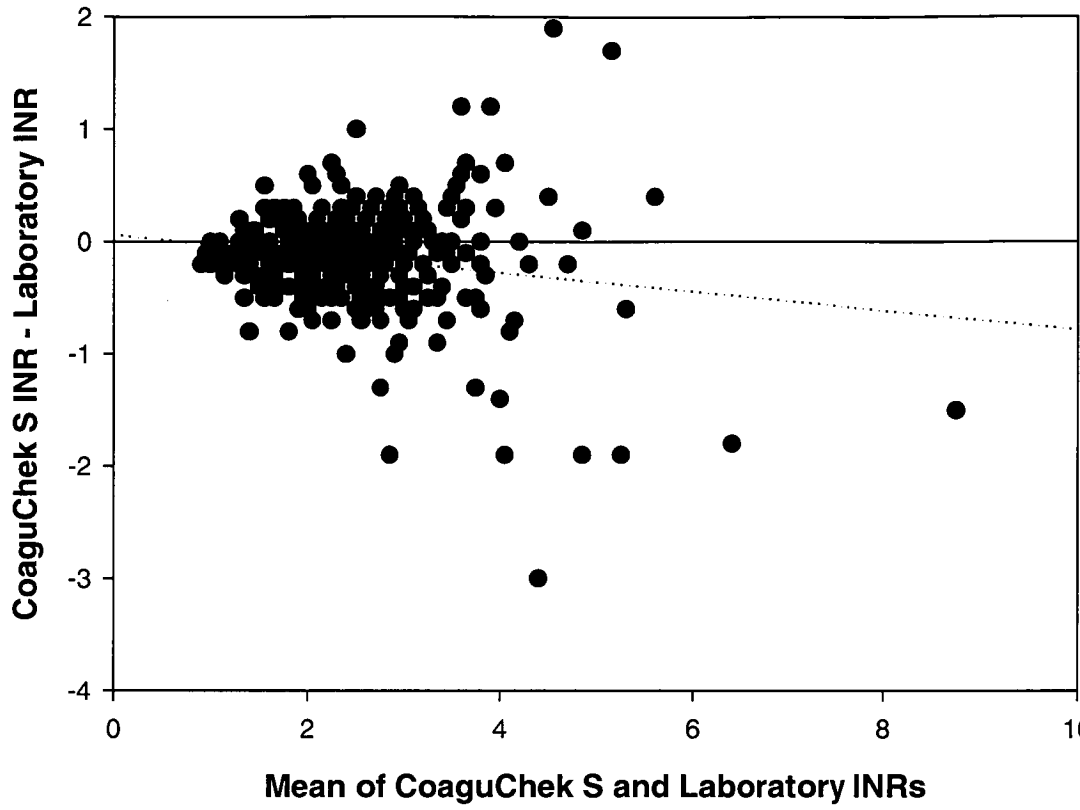



**Figure 23 Bland-Altman plot for CoaguChek S and laboratory INR values: General practice INR monitoring**

Clinical agreement against published expanded and narrow criteria [256] occurred 93% and 90% of the time, respectively. Table 38 shows the comparison of INR results determined by the laboratory and CoaguChek S. Overall, 88% of the dual measurements were within 0.5 INR units of each other. For laboratory INRs ≤1.9, 2.0-3.5 and ≥ 3.6, 97%, 90% and 57% of readings were within 0.5 INR units, respectively.

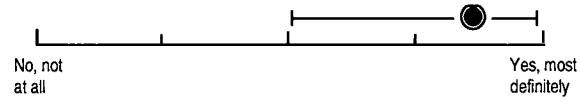
| Parameter | CoaguChek S | | Laboratory |
|---|---|---|---|
| INR (mean ± SD) | 2.39 ± 0.87 | | 2.54 ± 0.94 |
| Mean difference ± SD | | -0.08 ± 0.42 | |
| Percentage within 0.5 INR units | | 87.9 | |
| Percentage within 10% of laboratory INR | 55.1 | | |
| INR value, n (%) | 401 (100) | | 401 (100) |
| ≤ 1.9 | 127 (31.7) | | 96 (23.9) |
| Mean INR ± SD | 1.55 ± 0.31 | | 1.55 ± 0.26 |
| Mean difference ± SD | | 0.00 ± 0.23 | |
| Percentage within 0.5 INR units | | 96.9 | |
| Percentage within 10% | | 54.2 | |
| 2.0-3.5 | 239 (59.6) | | 259 (64.6) |
| Mean INR ± SD | 2.55 ± 0.38 | | 2.59 ± 0.26 |
| Mean difference ± SD | | -0.08 ± 0.34 | |
| Percentage within 0.5 INR units | | 90.0 | |
| Percentage within 10% | | 58.3 | |
| ≥ 3.6 | 35 (8.7) | | 46 (11.5) |
| Mean INR ± SD | 4.33 ± 0.93 | | 4.35 ± 1.14 |
| Mean difference ± SD | | -0.27 ± 0.82 | |
| Percentage within 0.5 INR units | | 56.5 | |
| Percentage within 10% | | 39.1 | |

**Table 38 Comparison of general practice CoaguChek S and laboratory INR results**

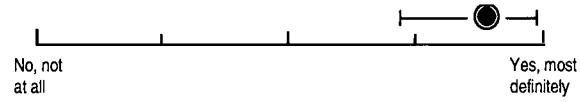
## 16.3 Evaluation questionnaire

A total of 19 questionnaires were returned from the 15 general practices. The survey responses are summarised in Figure 24.

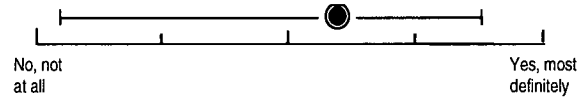
1. Was the availability of the CoaguChek S monitor useful to the clinical practice?



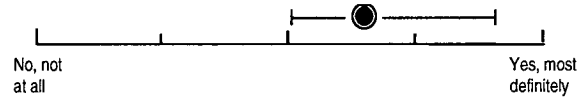

2. Was the CoaguChek S easy to use?



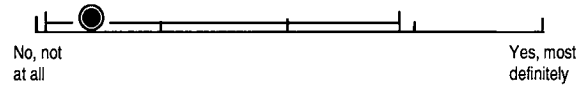

3. Were any difficulties experienced with the monitor?



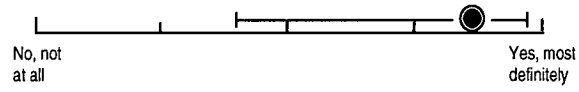

4. Were you confident in the accuracy of the monitor?



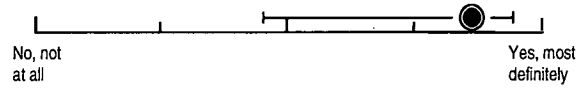

5. Do you think there would be any problems with having the monitor available in Australian medical practice?




6. Would you prefer to use the CoaguChek S monitor compared with conventional pathology practice?




7. Do you believe that your anticoagulated patients would prefer you to use the CoaguChek S monitor compared with conventional pathology testing?




8. Would you feel more confident in prescribing warfarin, knowing that you can routinely test your patient's INR values with a CoaguChek S monitor?

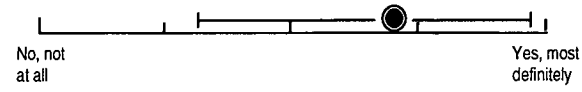



**Figure 24 Responses to the evaluation questionnaire- General practice INR monitoring**
Medians, with range lines plotted at the $10^{th}$ and $90^{th}$ percentiles

# CHAPTER SEVENTEEN: DISCUSSION

## RURAL GENERAL PRACTICE INR MONITORING

This study was unique in evaluating the CoaguChek S in a number of diverse settings (e.g. vastly different climatic conditions) and with many potential users. The performance of the CoaguChek S in the general practice setting was excellent, especially when considering that data was collected from many sites and was compared with different laboratories. Overall, 88% of dual INRs were within 0.5 INR units of each other. The correlation coefficients (r) from the various sites ranged from 0.84 to 1.00, with relatively little difference between the sites. All sites received the same training and support with the CoaguChek S monitor, so this is a good indication of the portability and ease of use of the CoaguChek S system.

It is clear from both the Bland-Altman plot and the regression analysis that the CoaguChek S was most accurate when the INR was in the therapeutic range, with scatter becoming prominent at INR values above 3.5. Hence, it needs to be emphasised to clinicians that differences can exist between INR values from POC testing monitors and laboratory values, especially when the INR is elevated. [291] Other studies have similarly concluded that the CoaguChek S is an accurate and precise alternative to laboratory assessment of the INR at values < 4.0 and that the monitor is an efficient device with a low likelihood of errors during testing. [257]

Interpatient variability may explain some of the discrepant results with the CoaguChek S compared to laboratory. It has been noticed in accuracy studies from the anticoagulation clinic [301] described earlier in this thesis, that variability does exist, perhaps explaining the large variations in INR that occurred in a few

instances. All laboratories were accredited by the National Association of Testing Authorities (NATA), which requires a satisfactory performance in the external quality assurance program. Hence, lowering the risk of quality assurance issues being to blame from the laboratory.

The CoaguChek S was adjudged 93% accurate against expanded agreement criteria and 90% accurate against narrow agreement criteria. [256] This compares favourably with data from other previously published studies where the older model of CoaguChek monitor was found to be 90% accurate against expanded agreement criteria and 86% accurate against narrow agreement criteria. [256] Shiach et al. recently showed 98% and 97% agreement against expanded and narrow criteria respectively, with the CoaguChek. [272]

The results for the user questionnaire indicated that the doctors at the evaluation sites found the CoaguChek S to be useful and would prefer to use the CoaguChek S monitor compared to pathology. There were some difficulties experienced in its use, and training with appropriate follow-up and ongoing external quality control are essential if the monitor is to be widely implemented in general practice. The most common difficulty related to the volume of blood needed for a sample; the CoaguChek S machine requires a large drop of blood (40μL) compared to conventional blood glucose monitors (5μL). This needs to be addressed during training as a squeezed finger can give errant results.

The GPs were generally confident in the accuracy of the monitor and foresaw little problem with having it available for widespread use in general practice. Doctors also indicated that their patients preferred POC testing. There was also a trend towards doctors feeling more confident in prescribing warfarin, given access to the CoaguChek S.

In conclusion, any limitations of the CoaguChek S monitor would seem to be far outweighed by the potential benefits to patients taking warfarin. The availability of an instant INR value improves the safety of a recognised high-risk drug for adverse events. [302] Clearly, any approach that improves the safety and efficacy of anticoagulation has enormous potential in terms of both beneficial clinical outcomes and cost savings to the health care system in the management of patients with either VTE or AF. This is particularly relevant in rural or remote settings because of the lack of access to pathology services. Our results indicate that the CoaguChek S has the potential to lead to safer and more effective anticoagulation, and therefore to better care of patients in rural and remote areas of Australia.

The use of POC testing for anticoagulation has the potential to revolutionalise the management of patients on warfarin therapy. As noted by Bhavnani and Shiach [303] the remaining issue to be addressed is how we can best offer high quality external quality assurance. In the meantime we must be ready to embrace this technology while still appreciating its limitations.

# CHAPTER EIGHTEEN: INTRODUCTION

# MODELS OF ANTICOAGULATION MANAGEMENT

## 18.1 Anticoagulation clinics

Anticoagulation clinics in the United States have been shown to facilitate and improve long-term anticoagulation management for referring primary care physicians. Several reports document improvement in anticoagulation control when managed in a clinic setting, [304-312] such as better warfarin dosage regulation, increased time in the therapeutic range, improved patient compliance through continuous regulation and early identification of risk factors (drug interactions, clinical conditions) for bleeding and thrombosis. [313] Gaughan et al. [314] reported an increase in the use of warfarin in a community hospital with the establishment of an anticoagulation clinic.

A study by Beyth et al. [315] reported fewer adverse events in elderly patients who were randomly assigned to an anticoagulant clinic, and the rate of bleeding was lower with an inpatient anticoagulant-consultation service. [314] Randomised trials have found that specialised, multidisciplinary clinics achieve better management than usual care for anticoagulated patients. [316] In another study, anticoagulation clinic patients were more satisfied with and more knowledgeable about their warfarin therapy. [317] These trials are consistent with other observational studies that also found improvement in INR control, satisfaction or outcomes with anticoagulation clinics. [304-312]

## 18.2 Patient self-monitoring and self-management

Patient self-monitoring, [287] and patient self-management [251, 262, 282-284, 286, 287, 303, 315, 318-323] have been proposed as solutions to reducing the risks of anticoagulant misadventure. [132] Sawicki et al. [282] found improved INR control in patients randomly assigned to an intensive patient education program that included self-management of anticoagulation therapy. Table 39 displays outcomes of trials involving patient self-monitoring and self-management.

Self-adjustment of warfarin therapy is analogous to self-adjusted insulin dosing according to a pre-specified sliding scale; [318] this practice in diabetic patients was associated with improved outcomes by delaying the onset or slowing the progression of vascular and neurological complications. [251] A major cause of unstable anticoagulation is poor patient compliance, [289] and self-adjustment of warfarin dosing has the potential to improve compliance by allowing active participation and increasing accountability with respect to the patients' own health. [251] Patients in a trial of patient self-management preferred this type of management compared to physician managed care. [251]

A study by Anderson et al. [281] in 1993 found that patients receiving long-term anticoagulant therapy achieved a high rate of clinically important agreement between self-measurements of the INR with the use of a portable monitor and laboratory INR results, and patients strongly preferred using the portable monitor. [281] The study concluded that the use of the portable monitor as the primary method for measuring the INR could be recommended in selected patients receiving long-term anticoagulant treatment.

| Study | Study Design | Study Groups | No. of Patients | Time in Range, % INR % Time | Major Hemorrhage, % per patient-year | Thromboembolism, % per patient-year | Indications |
|---|---|---|---|---|---|---|---|
| White[140] 1989 | RCT | | | | | | |
| | | PST | 23 | 93 | 0 | 0 | Mixed |
| | | AMS | 23 | 75 | 0 | 0 | Mixed |
| Anderson[139] 1993 | Inception cohort | | | | | | |
| | | PST | 40 | 74 | 0 | 0 | Mixed |
| Beyth[141] 1997 | RCT | | | | | | |
| | | PST | 162 | 56 | 5.7 | 9 | Mixed |
| | | UC | 163 | 33 | 12 | 13 | Mixed |
| Ansell[145] 1995 | Observational cohort | | | | | | |
| | | PSM | 20 | 89 | 0 | 0 | Mixed |
| | | AMS | 20 | 68 | 0 | 0 | Mixed |
| Bernardo[146] 1996 | Observational | | | | | | |
| | | PSM | 216 | 83 | NA | NA | Heart valves |
| Horstkotte[147] 1996 | RCT | | | | | | |
| | | PSM | 75 | 92 | 4.5* | 0.9 | Heart valves |
| | | UC | 75 | 59 | 10.9* | 3.6 | Heart valves |
| Hasenkam[142] 1997 | Observational matched control | | | | | | |
| | | PSM | 20 | 77 | NA | NA | Heart valves |
| | | UC | 20 | 53 | NA | NA | Heart valves |
| Sawicki[148] 1999 | RCT | | | | | | |
| | | PSM | 90 | 57/53† | 2.2 | 2.2 | Mixed |
| | | UC | 89 | 34/43† | 2.2 | 4.5 | Mixed |
| Kortke[149] 2001 | RCT | | | | | | |
| | | PSM | 305 | 78 | 1.7 | 1.2 | Mixed |
| | | UC | 295 | 60 | 2.6 | 2.1 | Mixed |
| Watzke[150] 2000 | Prospective controlled | | | | | | |
| | | PSM | 49 | 86 | 4‡ | 0 | Mixed |
| | | ACC | 53 | 80 | 0 | 0 | Mixed |
| Cromheecke[151] 2000 | Randomized crossover | | | | | | |
| | | PSM | 50 | 55 | 0 | 0 | Mixed |
| | | ACC | 50 | 49 | 0 | 16 | Mixed |

RCT indicates randomized controlled trial; PST, patient self-testing; PSM, patient self-management; AMS, anticoagulation management service; UC, usual care; and Mixed, mixed indications.
*Major and minor bleeding.
†Time in target range at 3 and 6 mo.
‡Percentage of episodes in 49 patients.

**Table 39 Studies of patient self-testing and self-management of anticoagulation.**
Reproduced from Hirsh et al. [73]

According to Cromheecke et al. [284] self-management of oral anticoagulant therapy with portable INR monitors may result in a more individualised approach, increased patient responsibility and enhanced compliance, which may lead to improvement in the regulation of anticoagulation. Another advantage noted was that patients could do the test at home (saving travel and time during working hours) and would be less dependent on their anticoagulant clinic. [284] However, this could potentially lead to a poorer regulation of oral anticoagulant therapy, due to a lack of

professional guidance. The study by Cromheecke et al., showed that there was no significant difference in the overall quality of anticoagulation between patients managed by an anticoagulation clinic and those patients managing their own warfarin therapy. Patients were within a range of 0.5 units from their therapeutic INR target range for 55% and 49% of the treatment period during self-management and anticoagulant clinic management, respectively.

A patient satisfaction assessment showed superiority of self-management over conventional care. It was concluded that self-management of INR with portable INR monitors is feasible and appeared to result in control of anticoagulation that is at least equivalent to management by a specialist anticoagulation clinic. It was also found in this study that there was some variation between INR results from the portable INR monitor and laboratory testing. However, the variation was not larger than the variation encountered between different laboratories measuring a single sample. [278] Although it was noted that a certain 'type' of person was more likely to participate in this study (despite being a randomised study), namely younger patients, other studies have found that all patients who are able to lead an independent and self-supporting life are in principle capable of self-management of anticoagulation, irrespective of education or social status. [285, 323, 324] "Self-management of anticoagulation may be considered as a novel, patient friendly and effective strategy to improve long-term treatment with anticoagulant agents." [284]

Another study of self-management of oral anticoagulation found that selected patients on chronic anticoagulation therapy can acquire a satisfactory ability for self adjustment of oral anticoagulant therapy dose, even without specific training related to dosage adjustment (patients still completed training related to using their monitor). [285] It was estimated in one German study [323] that 50-60% of all patients on anticoagulant

therapy were suitable for self-management. As noted by Vink et al., "INR home testing appears to be a safe and efficient anticoagulation control method which results in a higher percentage of target range values compared with the conventional laboratory-based testing regimen." [325]

## 18.3 Pharmacist-led anticoagulant management

POC testing in pharmacies has two main functions. The first is in disease screening or risk assessment (e.g. blood glucose or cholesterol determination). The second function is in monitoring and management of chronic diseases and medicines used to manage these conditions, as with anticoagulant therapy.

The increasing number of patients on warfarin and concerns over the ability of conventional health services to cope is one of the reasons for the expansion of POC testing, and moves to find alternative models of service provision within primary care for anticoagulated patients. Many models of anticoagulant management have been proposed in the literature; innovative models such as community and general practice based anticoagulant clinics run by nurses [307] and pharmacists, [313, 326-332] patient self-monitoring, [287] and patient self-management [251, 262, 282-284, 286, 287, 303, 315, 318-323] have been proposed as solutions to reducing the risks of anticoagulant misadventure. [132] Very few studies have studied the effect of community pharmacists' involvement in anticoagulant management. [333]

The public is becoming increasingly familiar with community pharmacists expanding their role in providing a range of health care related services. In addition to the traditional role of providing advice on prescribed and over-the-

counter medications, pharmacists are involved in services such as blood pressure screening, [334] cholesterol measurement [335, 336] and home medicines review. [337]

POC testing allows pharmacists to overcome the obstacle of lack of access to laboratory results, providing immediate availability of relevant laboratory tests that can be used for clinical decision-making. [338] POC testing provides opportunities for pharmacists to expand their activities and to generate income. [338]

Community pharmacists are ideally placed to assist GPs in the management of anticoagulated patients in the community. Pharmacists' undergraduate experience covers pharmacology, pharmacokinetics and drug interactions, and this knowledge can be used to predict disease and drug interactions with warfarin. Pharmacies also have instant access to patients' medication records. It would seem that pharmacists, being the most readily accessible health professional in the community setting, could fulfil a valuable role in ensuring the safe and effective use of anticoagulant therapy by establishing an INR monitoring service. Despite this, relatively few community pharmacies have undertaken anticoagulant monitoring, and this finding is not only restricted to Australia.

## 18.4 Rural health

There is clear evidence of the poorer health status of rural and remote Australians. [339, 340] Overall, average death rates in rural and especially remote areas are higher than in metropolitan areas. [340] The mortality rates in rural and remote areas are higher for many major conditions, including diabetes, cardiovascular disease and asthma. For instance, it has been shown that the lower

socio-economic groups and populations living outside capital cities have improved their cardiovascular disease risk factor profile in recent times, but the relative disadvantage compared with the higher socio-economic groups and major cities persists. [341-344] There have been calls for the immediate introduction of measures to ensure optimal treatment of cardiovascular risk factors and acute coronary events in such populations. [342, 343, 345] Access difficulties due to distance, time, cost and transport availability in rural and remote regions are amplified by the shortages and uneven distribution of health facilities and health professionals. [346]

Rural areas have a lack of GPs, pharmacists and other health care professionals. Thus it is difficult for members of rural communities to access specialist treatment. This also means that those health care professionals in the region will be very busy, while this is also compounded by the closure of hospitals and other health care facilities.

Currently, there is an undersupply of rural doctors and this lack of supply is pivotal to the delivery of healthcare to rural and remote communities.[347] A characteristic of modern medical treatment is the progressive growth in specialist medical services, both for assessment and treatment. Highly specialised services (such as pathology services) can be offered only in cities and large population centres, and the growth of these services can lead to a parallel increase in local disadvantage for people in small rural and remote communities. [348]

The first study described in this thesis has indicated that Australian doctors believe that the availability of portable INR monitors would assist with the management of anticoagulated patients. [246] This is particularly relevant in rural or remote settings because of the lack of access to pathology services. It is not

uncommon for doctors from rural or remote regions to have to wait two days for pathology results. The doctors also indicated that the availability of portable INR monitors might influence their decision to use warfarin for stroke prevention in AF. There appear to be two main reasons for the low use of antithrombotic therapy for stroke prevention in AF: inconvenience and physicians' fear of haemorrhage. [194-196, 201] Compared with urban patients, rural patients often travel further to have their INRs monitored, and this greater inconvenience may contribute to their lower use of warfarin. [349]

## 18.5 Aims and objectives: Rural community pharmacy-based INR monitoring

Having identified a paucity of data surrounding the use community pharmacy-based INR monitoring, the aim of the project was to assess whether rural pharmacist involvement in the management of targeted 'high risk' patients (i.e. those receiving warfarin therapy) has the potential to lead to safer and more effective anticoagulation, and is valued and welcomed by patients and their GPs.

# CHAPTER NINETEEN: METHODS

# RURAL COMMUNITY PHARMACY-BASED INR MONITORING

## 19.1 Rural pharmacies and training methods

A convenience sample of rural pharmacists (PHARIA classification > 2; or if 1, defined as regional) was identified by SLJ through a composite of previous research activities with the research team and via contact through electronic means (*AusPharmList*). Pharmacies needed to have an area where POC testing within the pharmacy could be reasonably completed privately during normal workflow.

The pharmacists were trained in the use of the CoaguChek S INR monitor and given educational material relating to warfarin. [73] The training typically involved approximately two to three hours with the pharmacists discussing anticoagulation and the use of the INR monitor. Pharmacists were shown how to conduct INR tests and were also observed conducting tests on consenting subjects or pharmacy staff. Problems or difficulties encountered by the researchers (through previous research activities [301] and personal experience) were raised with the pharmacists and potential solutions to these difficulties were discussed. The pharmacists were provided with a laminated colour brochure on the INR monitor (Appendix 7) along with the investigators' contact details. Pharmacists were provided with INR monitors, tests strips and other consumables free of charge for the duration of the trial.

## 19.2 Laboratory and point-of-care methods for determination of INR

Local GPs were visited, given an information sheet (Appendix 10) and informed of the availability of the CoaguChek S INR monitor in their region, and were invited to refer their patients to the pharmacy for POC testing. During the visits to the GPs, SLJ discussed the accuracy of the CoaguChek S INR monitor and the use of this monitor in several overseas countries. SLJ also discussed previous research that had been conducted on the monitor and personal experiences surrounding its use.

Patients referred to the pharmacy or who were identified as taking warfarin were given an information sheet (Appendix 11) and gave written informed consent to undergo fingerprick testing at the pharmacy. Results of the testing, such as INR, time taken, outcome of test (Appendix 12) were recorded. All results were sent to the GP via a specially designed fax form (Appendix 13). Pharmacists and GPs were instructed that this type of testing was not to replace conventional pathology testing.

Patients could have two types of testing performed in the pharmacy: comparison testing was defined as pharmacy-based tests taken within four hours of conventional laboratory testing, and additional testing which was a pharmacy-based test with no direct comparison laboratory test taken. It was recommended to pharmacists that all results were recorded for patients in the standard warfarin booklet. The service was offered free of charge to patients for the duration of the trial. Pharmacies were remunerated at a rate of $4 per test for the duration of the trial.

## 19.3 Evaluations

The CoaguChek S INR monitor was left with each participating pharmacy for approximately three months. GPs and pharmacists were later sent an anonymous questionnaire (using a visual analogue scale) to evaluate the pharmacy-based INR monitoring. The extremes of the scale were marked with (0) "strongly agree" and (10) "strongly disagree". Median results with tenth and ninetienth percentiles were plotted to represent the responses to the evaluation questionnaires. Patients were given an anonymous satisfaction survey (Appendix 14) from community pharmacists after the completion of the INR monitoring trial.

## 19.4 Statistical methods

The INR values from CoaguChek S and the laboratory were compared using regression analysis. A Bland-Altman plot [280] was utilised to assess the magnitude of disagreement between the CoaguChek S and the laboratory. The accuracy of the CoaguChek S at INR values $\leq 1.9$, between 2.0-3.5 and $\geq 3.6$ was also evaluated.

# CHAPTER TWENTY: RESULTS

# RURAL COMMUNITY PHARMACY-BASED INR MONITORING

## 20.1 Pharmacy characteristics

A total of 22 pharmacies were identified and invited to participate in the project. Sixteen pharmacies agreed to participate and were visited by SLJ and trained to use the CoaguChek S INR monitor. The PHARIA classifications, number of tests and number of patients tested per pharmacy are listed in Table 40. Ten of the 16 (63%) participating pharmacies had Australian association of consultant pharmacists (AACP) accredited pharmacists as regular full-time staff members. Three pharmacies did not conduct any testing during the trial period. Reasons behind testing not being conducted included a 'lack of interest by patients in having additional testing done' and 'lack of time (at present) to implement the service.' This pharmacist expressed willingness to implement the service later, but time constraints associated with this study, did not allow this to happen. Another pharmacist cited pharmacists on holidays, store refits and the Christmas period as a reason for lack of implementation of the program.

| Pharmacy | PHARIA | No. Tests | No. Patients |
|---|---|---|---|
| Tas 1 | 3 | 171 | 14 |
| Tas 2 | 3 | 17 | 2 |
| Tas 3 | 2 | 12 | 8 |
| Tas 4 | 4 | 58 | 27 |
| Tas 5 | 3 | 37 | 6 |
| Tas 6 | 5 | 31 | 17 |
| Tas 7 | 4 | 0 | 0 |
| Nth QLD 1 | 3 | 37 | 9 |
| Nth QLD 2 | 3 | 11 | 3 |
| NSW 1 | 1 | 35 | 17 |
| NSW 2 | 5 | 50 | 17 |
| NSW 3 | 3 | 30 | 6 |
| NSW 4 | 3 | 0 | 0 |
| SA | 5 | 18 | 9 |
| WA 1 | 4 | 11 | 2 |
| WA 2 | 1 | 0 | 0 |
| **Total** | | **518** | **137** |

**Table 40 PHARIA characteristics and number of tests per participating pharmacies**

## 20.2 Testing characteristics

Characteristics of the testing and of the patients who were tested are described in Table 41. A total of 518 tests were conducted in the pharmacies and 137 different patients were tested. Over three-quarters of the pharmacy based tests were taken

in addition to conventional laboratory testing, as opposed to having comparison tests.

| Testing characteristics | Result |
|---|---|
| Number of tests conducted | 518 |
| Tests per pharmacy median | 31 |
| Proportion of tests performed on female patients n (%) | 157 (30) |
| Number of patients tested | 137 |
| Tests per patient median | 2 |
| Proportion of female patients tested n (%) | 66 (48) |
| Age median (range) | 72 (23-100) |
| Test duration (minutes) median (range) | 5 (2-15) |
| Reason for use of warfarin (n=122*) | |
| Atrial fibrillation n (%) | 63 (53) |
| Valve replacement n (%) | 20 (16) |
| DVT or PE n (%) | 33 (27) |
| Other n (%) | 6 (4) |
| Number of chronic medical conditions median (range) | 3 (1-7) |
| Number of chronic medications median (range) | 5 (1-15) |
| Type of testing | |
| Comparison to conventional pathology testing n (%) | 120 (23) |
| Additional testing in the pharmacy n (%) | 398 (77) |

**Table 41 Characteristics of pharmacy based testing and patients involved**
*n=122 as reason for use not recorded in some cases

The majority of tests (67.0%) were in the expanded therapeutic range of 2.0-3.5, with over one-quarter (27.8%) being ≤ 1.9. The remaining tests (5.2%) were ≥3.6.

## 20.3 Accuracy analysis

One hundred and twenty pharmacy-based INR tests had comparison laboratory tests taken for which the results were made available to SLJ. The mean INR values for the laboratory and pharmacy-based tests are listed in Table 42. The pharmacy-based INR values were significantly correlated with the laboratory INR values ($r = 0.88$, $p < 0.0001$; Figure 25).

| Parameter | CoaguChek S | Laboratory |
|---|---|---|
| INR (mean ± SD) | 2.32 ± 0.77 | 2.32 ± 0.59 |
| Mean difference ± SD | -0.00 ± 0.38 | |
| Percentage within 0.5 INR units | 84.8 | |
| Percentage within 10% of laboratory INR | 76.0 | |

**Table 42 Comparison of pharmacy-based CoaguChek S and laboratory INR results**

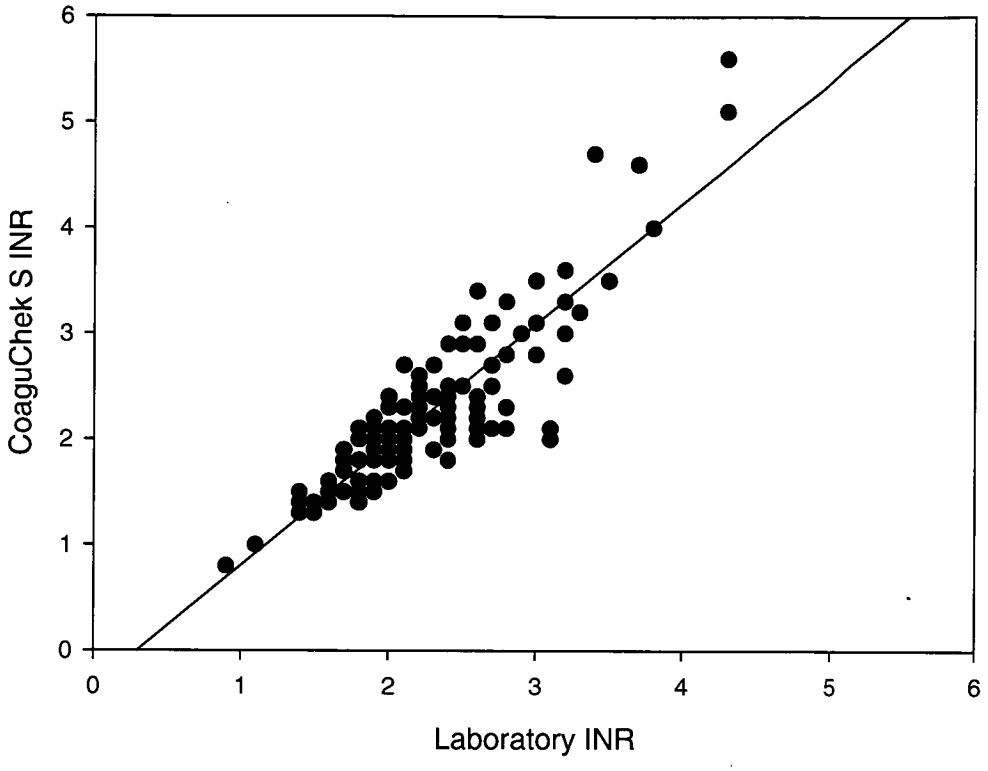



**Figure 25 Relationship between CoaguChek S and laboratory INR values: Pharmacy-based INR monitoring**

The Bland-Altman style plot shown in Figure 26 shows the difference between the two readings plotted against the average of the two readings. The pharmacy-based tests showed only slight variation compared with laboratory testing for INR values < 4.0.

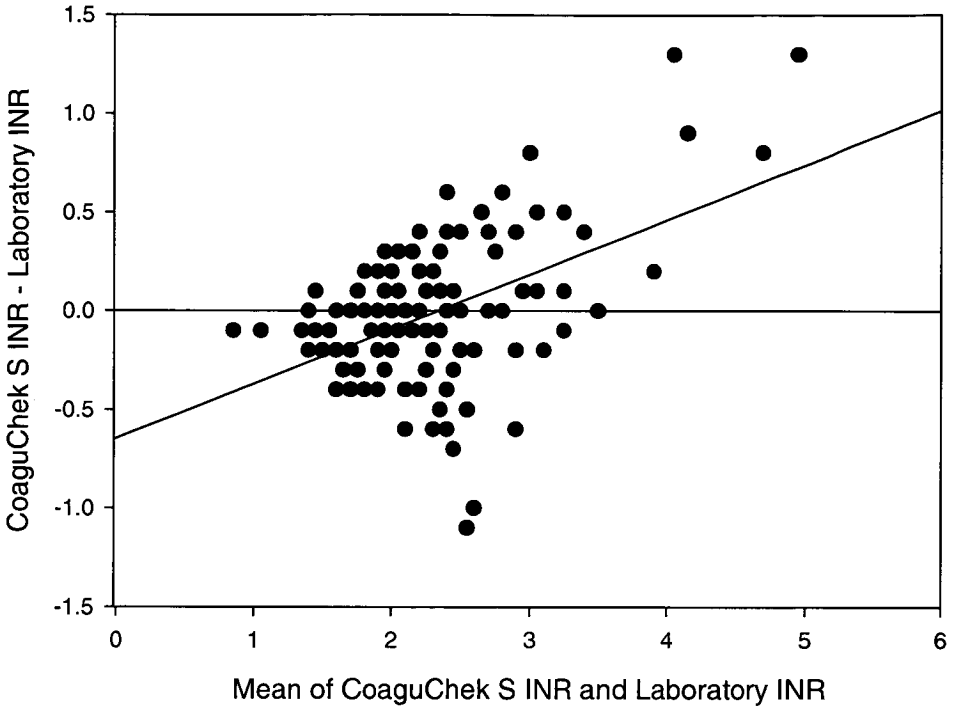



**Figure 26 Bland-Altman plot for CoaguChek S and laboratory INR values: Pharmacy-based INR monitoring**

The categorisation of laboratory and pharmacy-based INR values is displayed in Table 43. There was a significant relationship between the two methods ($\chi^2$= 130, df = 4, $p < 0.0001$). Discrepant categorisation of INR values from the laboratory and CoaguChek S occurred in 15% of the samples. That is, 85% (102/120) of CoaguChek S values were placed in the same nominal category as the laboratory INR. Seven and a half percent were falsely lowered with the CoaguChek S (corresponded to a higher laboratory reading) and the same amount was falsely elevated (corresponded to a lower laboratory result).

| | INR range | CoaguChek S INR | | |
|---|---|---|---|---|
| | | ≤ 1.9 (n=36) | 2.0-3.5 (n=76) | ≥ 3.6 (n=8) |
| **Laboratory INR** | ≤ 1.9 (n=33) | 82 | 18 | 0 |
| | 2.0-3.5 (n=82) | 11 | 85 | 4 |
| | ≥ 3.6 (n=5) | 0 | 0 | 100 |

**Table 43 Comparison of INR categories for CoaguChek S and laboratory**
Values given as percentage of laboratory readings

## 20.4 Clinical outcomes

Table 44 displays INR ranges and outcomes of the 398 additional pharmacy-based tests and whether this testing resulted in dosage changes. Eight and a half percent of additional testing conducted in the pharmacy resulted in a subsequent dosage change.

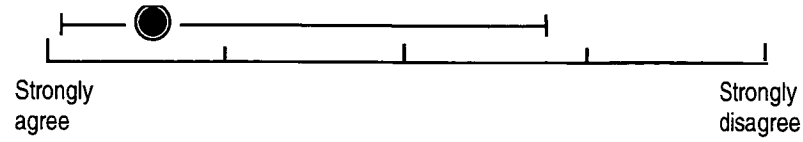
| INR range | Result (%) (n=398) | Dosage Changes | Result (%) (n=390*) |
|---|---|---|---|
| ≤ 1.9 | 27.1 | Dose increase | 5.9 |
| 2.0-3.5 | 68.1 | No change | 91.5 |
| ≥ 3.6 | 4.8 | Dose decrease | 2.6 |

**Table 44 Outcomes of additional testing conducted in the pharmacy**
*n=390 as some outcomes were not recorded

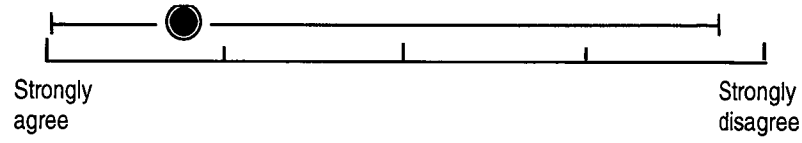
## 20.5 General practitioner evaluation

Figure 27 displays the responses to the evaluation questionnaire from the GPs. Responses were obtained from 15 GPs. Thirty GPs were caring for patients who had pharmacy-based testing, giving a response rate of 50%. The median responses from the GPs are positive in all but one question, with wide tenth and ninetieth percentiles reflecting some variable views on the pharmacy-based monitoring. However, the response to the evaluation question "I found the suggestions made by the pharmacist to be useful" was negative. The median response from the GPs to this question was 7. This feeling was repeated in some of the comments, as displayed in Table 45.

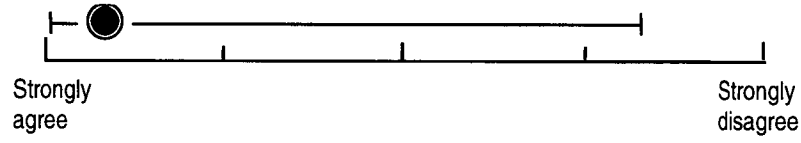
I found this to be a valuable service provided to my patient(s)



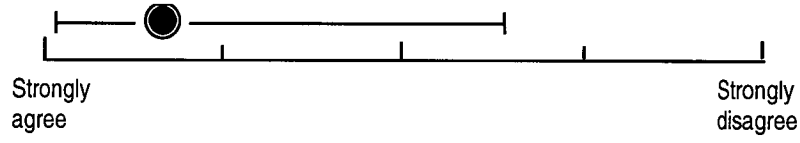

I would feel more confident in initiating or managing newly initiated patients on warfarin if this was a regular service



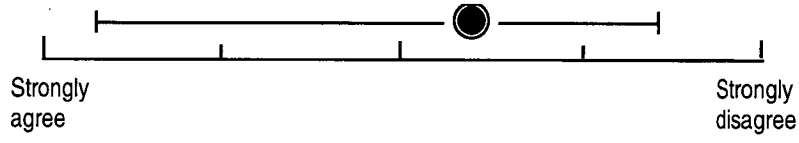

I received adequate feedback from the pharmacist




I believe that more patients would benefit from this type of service




I found the suggestions made by the pharmacist to be useful




I believe that my patient(s) found this to be a worthwhile service

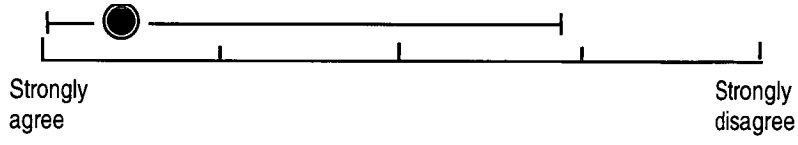



**Figure 27 Responses to the evaluation questionnaire: General practitioner evaluation of pharmacy-based testing**
Medians, with range lines plotted at the 10th and 90th percentiles

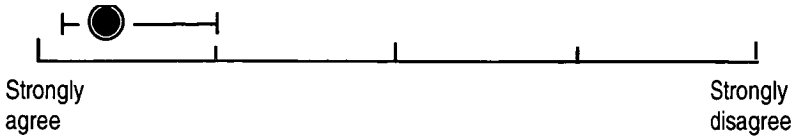
| |
|---|
| • Perhaps patients could have a card with INRs and the date to carry with them. |
| • Glad to be part of it, thanks. |
| • More suited for areas where no pathology service does home or nursing home visits. |
| • Seemed to reflect laboratory INRs. |
| • I do not need pharmacist input. |
| • Good service should be available through general practices and funded via medicare. |
| • What is the point in doing this via pharmacies, when the medications are initiated, prescribed and monitored by doctors? If pharmacists take on these functions, presumably they will have malpractice indemnity etc!! |
| • Discrepancy between laboratory INRs and pharmacy level suggests calibration of tests needs to be reset. |

**Table 45 Comments from responding general practitioners: Pharmacy-based testing**

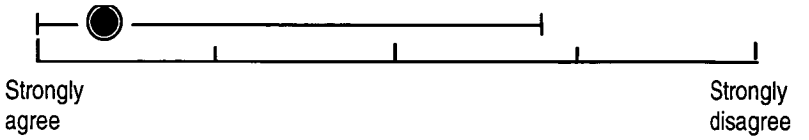
## 20.6 Pharmacist evaluation

Figure 28 displays the response to the evaluation questionnaire from the community pharmacists. Fifteen responses were obtained from 22 (68%) community pharmacists who were users of the INR monitor. The overall evaluation from the pharmacists was positive. The response to one question "I received positive feedback from the general practitioners", however, was less positive than the others. Comments from the responding community pharmacists are displayed in Table 46. Most comments reflected good patient feedback, the issue of training, time to conduct this type of service and the issue of remuneration. Four of the thirteen pharmacies that conducted testing have purchased or have been loaned monitors by SLJ and will continue to conduct INR testing in the pharmacies on an ongoing basis.

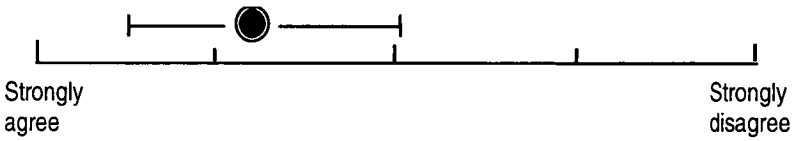
I found this to be a valuable service provided to my patient(s)



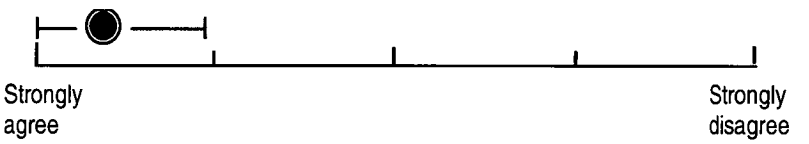

I would feel comfortable operating this service if it was ongoing



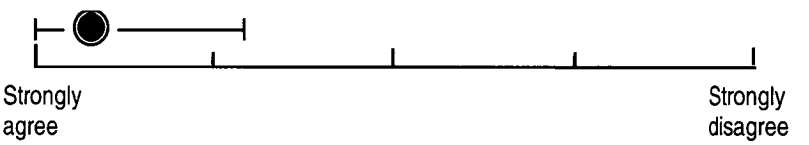

I received positive feedback from the general practitioners




I believe that more patients would benefit from this type of service




I believe that this service would increase the compliance of patients on warfarin




I believe that my patient(s) found this to be a worthwhile service

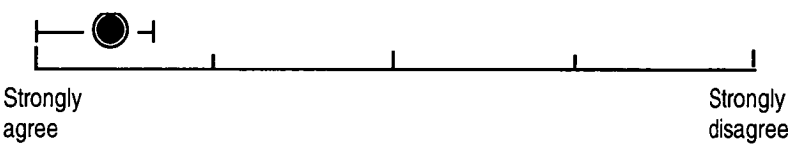



**Figure 28 Responses to the evaluation questionnaire: Pharmacist evaluation of pharmacy-based testing**

Medians, with range lines plotted at the 10th and 90th percentiles

| |
|---|
| • Training for technique in using the machine, very good for pharmacy, great to be able to offer another service to the customer |
| • Great addition to any community pharmacy practice. Especially useful for nursing home patients |
| • This type of service probably increases quality of warfarin treatment, not compliance. All our patients seem to be very compliant in taking the medication, some don't worry much about the INR-they leave that to the Dr. |
| • Blood in the pharmacy is a negative in these times of hepatitis and HIV. The machine was almost great. The temperature requirement of the strips and the device made measurements more time consuming. Everyone found instant feedback of the INR a great advantage |
| • Communication and rapport with patients a great benefit to both parties. It is an enjoyable service to provide to patients and they are appreciative of our efforts. It is nice to have the continued patient-pharmacist contact and the increased trust of the patient |
| • Time involved doing testing needs to be beneficial, i.e. cost involved. |
| • I found the experience worthwhile. Shane was a great educator and very thorough. Patients became or appeared to become more interested not only in their warfarin but other medications as well. A pleasure to be involved. I would encourage more of this sort of research. |
| • Good idea, but fiddly and time consuming. Well received by patients; more convenient. |
| • While a valuable, worthwhile service, time is taken to perform and discuss. So remuneration is of consequence for ongoing provision. |
| • Much appreciated by patients. Very accurate results compared with pathology |
| • Some patients found this service very valuable. I found it was great to sit down one-on-one with the patient and develop a rapport with them. |

**Table 46 Comments from responding pharmacists**

## 20.7 Patient evaluation

The responses and comments from patients to the satisfaction questionnaire are displayed in Table 47 and Table 48 respectively. Responses were received from 62 patients, giving a response rate from patients tested of 45%.

Most of the comments from patients reflected an appreciation of the convenience with using pharmacy-based testing. They seemed to be very happy

with POC monitoring but perhaps found it a barrier to utilisation of the service, that pharmacists were unable to adjust doses on the basis of these results. Some patients expressed views that governments or other organisations should pay for this type of monitoring. A number of patients compared the accuracy of the pharmacy-based testing with laboratory testing and went as far to include their results in their responses. Patients generally expressed a preference for fingerprick testing in their comments compared to the current invasive pathology testing.

| Response to questions | n (%) |
|---|---|
| *How satisfied are you with the monitoring conducted by your pharmacist?* | |
| Quite dissatisfied | 6 (10) |
| Indifferent of mildly dissatisfied | 2 (4) |
| Mostly satisfied | 13 (22) |
| Very satisfied | 37 (64) |
| *Has the monitoring provided by the pharmacist helped you to deal more effectively with your medication warfarin?* | |
| Yes, they helped a great deal | 33 (57) |
| Yes, they helped somewhat | 17 (29) |
| No, they really didn't help | 8 (14) |
| No, they seemed to make things worse | 0 |
| *Which type of testing would you prefer?* | |
| Fingerprick testing at the pharmacy | 40 (66) |
| Fingerprick testing at the general practitioner's surgery | 6 (10) |
| Conventional pathology testing | 13 (21) |
| Unsure | 3 (5) |
| *Is there any other information you need, or would like, about warfarin but have not received?* | |
| Yes, there definitely is | 13 (23) |
| Yes, I think there is | 10 (18) |
| No, I don't think there is | 30 (53) |
| No, there definitely is not | 4 (7) |
| *Overall, how would you rate the quality of the service that you received from the pharmacist?* | |
| Excellent | 45 (76) |
| Good | 13 (22) |
| Fair | 0 |
| Poor | 1 (2) |

| Response to questions | n (%) |
|---|---|
| *Did you find the regular warfarin (INR) monitoring** | |
| Painful | 5 (8) |
| Informative | 13 (21) |
| Motivating | 1 (2) |
| A waste of time | 3 (5) |
| Interesting | 12 (19) |
| Annoying | 3 (5) |
| Convenient | 27 (44) |
| Beneficial | 28 (45) |
| *Do you think this service would be best provided in your home or at your local pharmacy?* | |
| Home | 13 (22) |
| Local pharmacy | 38 (64) |
| General practitioners' surgery | 8 (14) |
| *Do you think this service should be available to all patients on warfarin?* | |
| Yes | 57 (98) |
| No | 1 (2) |
| *If this were a regular service, would you be prepared to pay for it?* | |
| Yes | 32 (57) |
| No | 24 (43) |
| *If you answered yes to the previous question, how much would you be prepared to pay per visit?* | |
| $1-$5 | 20 (63) |
| $6-$10 | 8 (25) |
| $11-$15 | 4 (13) |
| $16+ | 0 |

**Table 47 Response to the patient satisfaction questionnaire-pharmacy-based testing**

Some responses do not total 62, because some respondents did not answer all questions

*Totals greater than 62 because respondents could indicate more than one response

| |
|---|
| • It is a very good idea to have an INR machine at the chemist on Saturdays for people that work five days a week. |
| • I used the fingerprick testing at the pharmacy for 2 reasons; to see what was involved and to compare that reading to the reading of pathology, the readings taken 10 minutes apart were fingerprick 1.9, pathology 2.2. |
| • I have only once used the pharmacist and that was by request. The reading was 2.8, which compared to 2.1 by the pathologist. Being a preference they do the testing at home. |
| • I find the prick test less painful and the instant result very pleasing. As I live at Lake Albert I would like to see the test available at our pharmacy here. I am elderly and disabled and need a test weekly and sometimes more often. |
| • Repat should pay, the first couple of goes I thought, hell this hurts, but then I got used to it. |
| • We have only been to the pharmacy once. We go to the pathology at Wagga base. The fingerprick test was fairly accurate i.e. 2.6 as against the path 2.9 a few days later. We have no car so if we could have it done in the home it would help. |
| • If the pharmacist had the authority to advise how much warfarin to be taken daily on INR reading, I would have no hesitation in using such a facility or paying a small fee. |
| • I only had 2 consultations-the first test aligned with the pathology results. The second test resulted in a reading much higher than the pathology dept. On doctors' instructions I ceased the pharmacy testing. |
| • 10 years ago, I had a heart valve operation and need my blood tested every two to three weeks, last year I had bowel cancer and had chemo that made my veins very hard to find, the finger prick was wonderful and I wished I could have it all the time. |
| • I am very pleased with the treatment I received, thank you |
| • As a pensioner, a small cash amount is feasible. The test at the pharmacy would reduce the load on surgery nurses, which may be appreciated |
| • I only visited our local pharmacy on the same day I had my INR tested at my local surgery; GP result 2.1 and pharmacy result 1.8 |
| • The only reason I would be reluctant to pay for an INR service is that I am a disability pensioner and I require regular (every 1-3 weeks) INR monitoring and will continue to do so for life. Pharmacy monitoring is extremely more convenient than using the limited resources of an already over-stretched local GP service |
| • The service at the pharmacy is excellent. |
| • The pharmacy tests are an added help for my health and our pathology system. |
| • It is great to know the results of the INR immediately, as with this monitor. The benefit of having this service provided at your local GP is that any dose adjustment (warfarin) |

| |
|---|
| could be made on the spot, not in several days, as is the situation at present. |
| • I am a 32 year-old life-long warfarin patient. I probably have another 50 years of blood testing. At times I have to be tested every two weeks. I find the whole process of going to the doctor and waiting all day for results expensive. Imagine how much I will spend on this in my whole lifetime. |
| • Very pleased with testing. |
| • Finger pricking eliminates the inevitable bruising caused by repeated attempts at conventional techniques. One visit required seven attempts to procure a sample. |
| • I am very keen to have INR testing available at home and at pharmacies but the variance in results obtained between the actual pathology test and the machine test had a variance of up to 20%. |
| • I have not been able to participate in enough tests to be absolutely sure. |
| • I understood the machine was sent to the chemist to see how it compared to conventional pathology testing it was almost spot on. If I was just on warfarin and had it checked every 6 weeks, the fingerprick method is quite OK and it should be done at the pharmacy. This would relieve the doctor from this extra work |
| • The portable warfarin monitor would be a great asset to purchase if it was accurate. It was very inconsistent in its results compared to that from pathology. |
| • Country towns, no GPs or takes 2 weeks to get in to have an INR, go to hospital and wait until someone can do the INR. It then misses the courier, and the blood is over one-day old before it leaves the hospital to be tested. Apart from the schedule fee to get an INR done, we are charged again when you can get an appointment to get the result-often 4-5 days later. |
| • If you are on warfarin fulltime & need INRs weekly, it is impossible to get doctor appointments etc. to have blood taken & then to get the result you have to get another appointment and pay again. Country towns' with minimal doctors & pathology services you are risking people's health. This INR system/machine is brilliant, convenient & vital in isolated & small towns. Pay-cost? – I do not know? Very messy when you have to put claims in weekly and you have to fax as your town has no medicare office etc. |

**Table 48 Comments from patients: Pharmacy-based testing**

## 20.8 Case studies

The following three cases have been documented by participating community pharmacists in order to show some clinical outcomes of pharmacy-based testing in each of these cases.

Mr AB arrived at Tasmanian pharmacy no.4 late one Friday afternoon. Mr AB normally resides in inner city Sydney and is familiar with accessing pathology services when it is convenient for him. He asks the pharmacist where the local pathology service is, so he can "get his warfarin done". The pharmacist tells Mr AB that this small rural town's pathology services cannot be accessed after lunchtime on Friday. Fortunately for Mr AB, the pharmacist is able to obtain an INR result for him. The pharmacist obtains a past medical history from Mr AB of an aortic valve replacement in 1986, glaucoma, hypercholesterolaemia, and dyspepsia. Mr AB was using the following medications, in addition to warfarin: bimatoprost eye drops daily, simvastatin 40mg daily and pantoprazole 40mg daily. The pharmacist obtains a fingerprick sample of blood from Mr AB and a minute later an INR reading of 5.2 (target range: 2.5-3.5) was obtained from the CoaguChek S monitor. His warfarin dose had been increased about one week previously from 3.5mg daily to 5mg daily. The local general practice was very supportive of the pharmacy participating in this project and was contacted with a subsequent appointment made for Mr AB. As a result of this, his warfarin dose was reduced to 4 mg daily. Mr AB was also advised by the doctor to have a follow-up test on Monday in the next town he was to visit.

Interestingly, Mr AB's partner was also taking warfarin.

Mrs AB's past medical history included stroke, hypertension, arthritis and AF with a pacemaker fitted. Her current medications were warfarin 1mg daily, digoxin 250mcg daily and candesartan 8mg daily. Mrs AB's INR result was 3.2 (target range 2.0-3.0). On questioning, her last INR was taken some months ago with the results not known but considered 'stable'. The local GP consulted with her and reduced her warfarin dose to an alternating dose of

0.5mg/1mg daily. Like her husband, she was advised to have a follow-up pathology test taken on Monday. The couple were counseled by the pharmacist about dietary changes, especially whilst on holiday, that may affect the response to warfarin therapy, compliance with therapy, and the need for regular INR testing.

Ms LD was a young indigenous woman who has been taking warfarin for approximately six months for recurrent thrombosis. She had been increasingly non-compliant with therapy and "no-shows" for appointments with her GP were increasing. The pharmacist (Tasmanian pharmacy no.5) encouraged Ms LD to have fingerprick testing at the pharmacy using the CoaguChek S INR monitor, explaining to Ms LD that he could obtain a result quickly and any subsequent dosage changes could be promptly discussed with her GP. Ms LD's INR over the previous three months had ranged from 1.2-1.4 (target range: 2.0-3.0). Since accessing the INR monitoring in the community pharmacy, her dosage of warfarin had increased from 1mg daily to 3mg daily, with INR results consistently in the therapeutic range. Ms LD attends the pharmacy weekly and appears more compliant with her therapy.

# CHAPTER TWENTY ONE: DISCUSSION

## RURAL COMMUNITY PHARMACY-BASED INR MONITORING

This project was designed to test the feasibility of community pharmacy-based INR monitoring in rural Australia. We also wanted to gauge the acceptance of this type of service by community pharmacists, GPs and patients. The pharmacies were taken from all states of Australia, except for Victoria, and had PHARIA classifications ranging from 1 (regional) to 5, giving a broad spread of rurality. We recruited a large number of pharmacies (16) for a study of this type and the pharmacists involved conducted a large number of tests (518) on 137 patients.

This is the first completed study assessing the feasibility of community pharmacy-based INR monitoring. The author are aware of only one other study being conducted in Australia (Andrew McLachlan, University of Sydney) [350] using portable INR monitors in community pharmacies.

Utilising the CoaguChek S INR monitor in a community pharmacy has shown the monitor performs accurately compared to conventional laboratory testing. Previous studies described in this thesis have obtained correlation coefficients (r) of 0.90 in an anticoagulation clinic [301] and r = 0.89 in general practices, [258] compared with r = 0.88 in this study. Other studies have shown that the CoaguChek (previous version of INR monitor) and CoaguChek S devices produce INR values that are highly correlated with laboratory INR values (r = 0.91 - 0.97). [256, 259, 278, 291, 293, 294]

Eighty-five percent of all dual measurements were within 0.5 INR units in this study, which compares well to the figure of 79% reported by Douketis et al., [256] and 83% described earlier in this thesis in an outpatient anticoagulant clinic.

[301] This study also found that 76% of all comparison tests were within 10% of the laboratory value. This compares exceptionally well with other studies described in this thesis which have shown results of 55% of results within 10% of the laboratory in general practices [258] and 44% in an anticoagulation clinic. [301]

This study was unique in evaluating the CoaguChek S in a number of diverse settings and with many potential users. The performance of the CoaguChek S in the community pharmacies setting was excellent, especially when considering that data was collected from many sites and was compared with different laboratories. Previous studies have found that the variation between portable INR monitors and laboratory was not larger than the variation encountered between different laboratories measuring a single sample. [278] To my knowledge, this is the first published study comparing the accuracy of the CoaguChek S INR monitor in comparison to laboratory testing in a sample of community pharmacies.

The pharmacy-based testing has shown that over 30% of patients had INRs outside of an expanded therapeutic range, our population of tested patients compares well with previous research, that has shown that approximately 60-70% of patients will have INR value in the target range. [287, 351, 352]

In nearly 10% of cases the additional testing conducted in the pharmacy resulted in a change in therapy. Clinical decisions were made (generally followed by pathology testing in the next day or so) on the basis of results of tests based in the pharmacy. It is difficult to quantify the impact that the changes in therapy had on clinical outcomes. Examples of these changes on therapy are documented in three case studies. A limitation of the study was that the pharmacists, in most cases, recorded only dosage changes and not clinical or actual outcomes, although

the study was not designed to assess clinical outcomes. Therefore, a formal cost analysis of changes in therapy due to additional testing is beyond the scope of this study. However, it is likely the availability of POC testing in community pharmacies may have a large impact on clinical outcomes if pharmacy-based testing is utilised in rural areas. If further implementation of community pharmacy-based INR monitoring is undertaken, systems for recording of clinical and actual outcomes should be developed to analyse the clinical effects of these types of services.

The clinical impact of the pharmacy-based testing was unable to be fully assessed, although it was made known to SLJ that there were a number of instances where the availability of the pharmacy-based INR monitoring appeared to have potentially large clinical impact. Several of these instances are documented in the three case studies described in the Part two: results section of this thesis. We were made aware of other instances of appeared benefit apart from these three case studies, but the documentation surrounding these other cases was often lacking.

Little research has been conducted in regards to recommendations made to patients when they are traveling, and little is also known of clinical outcomes of anticoagulated patients when traveling. The first two case studies described elevated INR results in two patients who presented to a community pharmacy when traveling. The lack of access to pathology services for patients who are traveling may adversely affect their anticoagulant stability. [353] Time, cost, access, and convenience factors in organising pathology testing for patients traveling in rural and remote regions may be barriers to stable anticoagulant control. A study

by Pubentz et al. noted lack of access to monitoring as a contributing factor in increased complication rates amongst anticoagulated patients. [354]

The issue of poor compliance in regards to regular monitoring, as observed in case 3, has been raised in a number of studies as a reason for inadequate control of anticoagulant therapy. [327, 355] Studies have shown that structured POC monitoring and education programs have improved compliance with monitoring and understanding of anticoagulant treatment. [327, 354, 355] A study by Arnsten et al. reported that non-compliant patients were more likely to feel dissatisfied with their treatment, felt more burdened by taking warfarin and perceived fewer health benefits from the therapy. [355] Education of the patient (case 3) by the pharmacist, combined with less invasive and more convenient monitoring, appeared to have ameliorated these concerns and improved compliance with warfarin therapy in this case.

Further research needs to be conducted on the impact of community pharmacy conducted INR monitoring on patient care and outcomes. Most studies have shown that POC testing is beneficial when combined with changes in healthcare delivery systems. [338] Reports of POC testing used by pharmacists in anticoagulation clinics appear to verify that noted by the pharmacists in this project, that testing should be part of a larger program, [338] such as comprehensive anticoagulant education. POC testing must be associated with systems designed to efficiently and properly use the results and monitors. All of the studies of POC testing have only improved clinical outcomes when associated with comprehensive disease management. [338]

A response rate of 45% was obtained from the anonymous self-administered patient satisfaction surveys. The response rate to the surveys is

limited due to the anonymity of the survey and only one copy was given to patients with no reminder survey given. The authors are therefore unaware of which patients returned surveys, due to the delivering of surveys to patients from the community pharmacists, which was hoped to increase response rate. [356]

Advantages of self-administered surveys are that they help to eliminate interviewer bias and personal or embarrassing questions may be answered more frankly. [357] However, due to a response rate of less than 70%, there may be some non-response bias in the results of the satisfaction survey. [358] However, it has been demonstrated that, in general a response rate of above 40% in postal questionnaires is acceptable. [357] Mazor et al. have suggested that more satisfied patients are more likely to respond than less satisfied patients, [359] although we are unsure in our case if less satisfied patients were less likely to respond. Further qualitative research should be conducted assessing underlying themes and attitudes towards pharmacy-based INR monitoring.

The question that needs to be answered is whether this service meets the needs and expectations of patients. Patients' assessments of care have been advocated as an essential component of quality assessment. [360] The quality of the service was rated as good or excellent in nearly all cases. In the majority of cases, patients were very satisfied with the service provided, with a small number of patients dissatisfied or indifferent. It is unlikely that they were dissatisfied with the conduct of the pharmacist, as 98% of patients said the quality of the service was good or excellent. However, it may reflect a lack of pharmacist ability to adjust dosing and the testing may have been seen as a futile effort as indicated in some of the comments. Patients may be suspicious of the professional motives or

had negative feedback from their GP, and they may feel their needs are not being addressed in the design and implementation of services offered. [361]

Importantly, the majority of patients indicated that the pharmacy-based monitoring helped them deal more effectively with warfarin. This emphasises the ability of pharmacists to educate patients regarding their anticoagulant therapy, and in fact the effects of education delivered through pharmacy-based INR monitoring may have larger long-term impacts on compliance and anticoagulant-related misadventure. [327]

Sixty-four percent of patients indicated that they preferred pharmacy-based INR testing, which reinforces the consumer-led need for pharmacy-based INR monitoring to be available to patients receiving anticoagulants. Importantly, nearly all patients said that this service should be available to all patients receiving warfarin. This reinforces that this program is seen as beneficial from the patients' perspective and they see a need for this to be available to everybody. Some patients commented regarding the accuracy of the pharmacy-based testing compared to laboratory testing. It would be interesting to know if patients knew the variation between laboratories and could put this into context in relation to the variation between laboratory and the pharmacy-based testing. Pharmacists and GPs were alerted to this variation in the initial training and visits, respectively. However, studies have shown that patients are not adept at relating the differences between numbers and subsequently relating these to clinical decisions. [362, 363]

It is a limitation of the study and room for further research that nearly one-third of patients indicated that there was more information that they would like about warfarin. Structured education programs could be developed through community pharmacies and could complement pharmacy-based INR monitoring.

It is likely that pharmacy-based INR testing if implemented in community pharmacies would be part of larger education programs that may incorporate pharmacy based anticoagulation education, home medicines review, and identification/training of patients suitable for self-monitoring and self-management.

Nearly fifty percent of respondents indicated that they found the testing convenient and beneficial. This finding appears to be a common theme throughout the comments made by patients. Consumer-based studies of pharmacy services have revealed the main reason in using the local pharmacy is convenience. [364, 365] Patients receiving anticoagulation are often elderly, cannot endure long waiting times, and find traveling to hospitals or pathology laboratories difficult. [308] Pharmacies are usually located in convenient, accessible locations improving access for patients. A more convenient approach could be to provide long-term monitoring through accredited community pharmacies. In addition, liaison between GPs and pharmacists reduces the risk of toxicity and treatment failure, and patient knowledge can be improved through counseling. [308] The inability to make timely contact with the patient and the potential for misinterpretation of information conveyed by the GP has been shown to result in dosage errors. [251, 366, 367] As noted by Moffat, [368] the pharmacy profession has a great opportunity to use diagnostic testing to monitor patients' responses in assisting them to manage their chronic conditions and their prescribed medicines.

The testing process was well received by the community pharmacists; they felt confident delivering this type of service and found it be a valuable service that was delivered to patients. This appears to be a realistic ongoing service that could be implemented in community pharmacies in the future. [333] Pharmacists, however,

will need to address issues such as the need for separate counseling and consultation areas for testing, and occupational health and safety issues associated with handling bodily fluids. [369] Privacy in a community pharmacy has been cited as a potential barrier to conducting detailed consultations and therefore to obtaining appropriate advice and information, [361] although it has been suggested that patients may forgo privacy in favour of easier access to medications or to avoid examination. [370]

Ongoing quality assurance schemes will need to be developed to ensure pharmacy-based INR monitoring systems are of a high standard. As noted by Murdock, "There has to be seamless care between the primary and secondary settings so that the results found in pharmacies will dovetail in with those tests carried out by GPs or in hospitals". [371]

Responding pharmacists indicated that they thought that pharmacy-based INR monitoring would improve the compliance of patients on warfarin. In fact, pharmacist managed anticoagulation clinics have reported increased compliance after instituting education programs. [327]

There was a wide variation in the response from pharmacists' to the question "I would feel comfortable operating this service if it was ongoing". Overall, the response was positive, but the variation indicates there may be issues regarding delivering this service if current structures in community pharmacies persist. In their comments, pharmacists cited issues such as time constraints and remuneration as barriers to the delivery of these types of programs.

Pharmacists indicated that they received positive feedback from the GPs but the range of responses indicated that there was some less than positive feedback in some cases. A potential reason behind this variation in responses is

simply the pharmacists and GPs may not know each other well enough to have developed a trusting and respectful relationship. [361] This may be made more difficult by the trend in both professions, towards an increasingly mobile workforce, more locums and part-time working. [361] Future changes to funding arrangements for GPs and pharmacists may allow for greater collaboration between professions, and remuneration schedules should also reflect this.

The evaluation from the GPs was generally positive, but variation in a number of the responses was evident. A negative response was observed to the question "I found the comments made by the pharmacist to be useful". This may reflect barriers between general practice and pharmacies regarding perceived encroachment of pharmacy services on traditional general practice territory. [372] It has been suggested that models of interdisciplinary collaboration need to be implemented cautiously, as rapidly imposed change can create conflict and resistance. [373]

More formal integration of pharmacists into health care and the development of partnerships with GPs are crucial to the establishment of pharmacy-based INR monitoring. Professional barriers to the implementation of expanded pharmacy services have been identified in the literature. These include the "shopkeeper image" of community pharmacy. [372] GPs may be unaware of the training that community pharmacists have undertaken to perform these services.

The design of many community pharmacies has been identified previously as a concern for implementation of professional services. [372] It is recognised that a number of community pharmacies may have to undergo structural modifications to cope with the array of professional services that may be funded in the future. Negotiations should be encouraged with government departments for funding to

proceed with structural modifications in community pharmacies. This will allow community pharmacies to meaningfully contribute to primary health care management.

One of the recurring problems when pharmacy expands its role in providing other areas of health care is "who is going to pay". Patients are unlikely to pay (fully) for services that are provided free through GPs and pathology providers. Patients exempt from charges for conventional laboratory testing are not necessarily motivated, or do not have the resources, to obtain care from other sources. [370] Over 50% of patients expressed a willingness to pay for pharmacy-based testing, with over 50% of this group indicating a range of payment in the order of $1-$5. This service may be implemented in the short-term for those patients who are willing to pay for the service in its entirety.

The median testing time for pharmacists to conduct this type of service was five minutes in this pilot program. Pharmacists were instructed to record the time taken to conduct the testing and in the majority of cases' results were communicated to prescribers via the specially designed fax forms. If this program were implemented, streamlined communication channels would need to be designed to ensure results are communicated to GPs in a timely and accurate manner. It is accepted that if this program was to be implemented on a wider scale, monitoring may also encompass education and this process may in fact take a longer time. The answer lies in the pharmacy profession advocating remuneration for a primary role in anticoagulation management in the community setting. We propose a remuneration schedule similar to prescription medications and that pharmacists are paid a testing fee each time a test is conducted in the

pharmacy. This fee would encompass the cost of the testing strips and would be in the order of $15 per test ($6 per test strip, $1 mark-up and $8 testing fee).

Some limitations in training may need to be assessed in a training package that is assembled for community pharmacy. This may have been reflected in three pharmacies not conducting any tests during the study period. Although reasons cited for not performing testing were generally due to increased work implications from the testing, a lack of confidence with using the monitor may have contributed to these feelings. The majority of community pharmacists exhibited good clinical skills (63% were AACP accredited) and education regarding warfarin focused on pharmacology and dose adjustment, with literature provided in all cases. The University of Birmingham (www.bham.ac.uk) conducts a course for anticoagulant management for health professionals who are working in or aiming to work in anticoagulation clinics. This course is conducted over a three-day period, the focus of which appears to be on protocol development, history of anticoagulant management, warfarin use and pharmacology. We suggest the development of a distance-learning package could be developed covering this information with practical training on POC testing used in conjunction with this package to accredit community pharmacies to participate in INR monitoring. This type of warfarin monitoring service may improve patient outcomes and improve patient knowledge through education. Involvement of pharmacists in anticoagulant therapy is an accepted part of pharmacy practice in many countries.

Studies have found that elderly rural patients with chronic AF receive warfarin less frequently than urban patients, despite possessing a similar high-risk profile for stroke and fewer relative contraindications. [197, 349] This is partly attributable to the fact that GPs prescribe anticoagulant therapy for AF less

frequently than cardiologists, who are scarce in rural communities. [349] The impact of stroke is significant in rural, regional and remote areas, and this reflects difficulties in instigating preventive programs. [339]

# PART FOUR: IMPROVING WARFARIN INITIATION

## CHAPTER TWENTY TWO: INTRODUCTION

### 22.1 Adverse drug events

#### 22.1.1 Overview of adverse drug events

Despite calls for improvements in the use of pharmaceutical drugs, and better liaison between doctors, pharmacists and patients, [373] problems associated with the use of pharmaceutical drugs in society continue to be a significant public health burden. It has been estimated that problems associated with therapeutic drug use in Australia result in at least 80,000 hospital admissions annually (accounting for approximately 12% of all admissions to medical wards [374] - including at the RHH), [375] at a cost of around $400 million per year. [374] About one-half of these hospital admissions are considered to be avoidable.

> "Despite increasing attention to geriatric pharmacotherapy, there is an enormous need for additional research to improve the use of medications among older adults. The necessary research agenda encompasses much more than just the discovery of new drugs; better use of the current pharmacopoeia has great potential to improve the lives of older adults." [376]

In particular, adverse drug reactions remain a significant cause of hospital admissions [374] and unplanned re-admissions, [377, 378] frequently involving predictable high-risk situations (e.g. multiple drug use in the elderly) which are amenable to prevention through improved systems. [379] A study by Gurwitz et al. identified an overall rate of adverse drug events (ADEs) of 50.1 per 1000 person-years, with a rate of preventable ADEs of 13.8 per 1000 person-years. [380]

### 22.1.2 Transition from hospital to community care

Information gaps have been extensively documented in patients discharged from hospital. [381] Patients discharged from hospital are at high-risk of experiencing adverse effects; [382, 383] significant alterations to a patients' medication may occur in hospital. Patients may not take dosages appropriately after discharge and may not understand instructions appropriately. [367]

Hospitals' pharmaceutical care aims to provide a continuum for the Quality use of medicines (QUM) during the patient's entry into and treatment within hospital, and importantly re-entry into community or residential care settings. [384] In view of the increasing trends for earlier discharges, the need for continuity of care in relation to drug therapy is likely to have a significant impact on quality health outcomes. [384]

Successful discharge planning should be a centralised, co-ordinated, multidisciplinary process that ensures all patients have a plan for continuing care after they leave the hospital. "The transition from the hospital is often more threatening than the actual hospitalisation, and a plan must exist not only to provide for a continuum of care, but also to address the patient's immediate needs following discharge." [384]

### 22.1.3 Anticoagulant-related adverse drug events

Anticoagulants have been implicated in 10.2% of all preventable ADEs in ambulatory patients, [380] and 20% of ADEs in hospitalised patients taking cardiovascular drugs. [385]

Adverse events from warfarin use in Australia were estimated to cost over $100 million per annum in direct hospital costs alone (in 1992). [302] Reductions in the incidence of anticoagulant-related adverse events may be achieved through the following, as suggested by Murray and Callahan [376]

> "Many major improvements in medication use among older adults will also depend on closing the gap between knowledge and practice and increasing the ability of older adults to manage their medications."

The major complication of anticoagulant therapy is bleeding. [105, 118, 386] Based on estimates from randomised trials, the average annual frequencies of fatal, major, and total bleeding during long-term warfarin therapy are 0.6%, 3.0%, and 9.6%, respectively; these frequencies are approximately five times those expected without warfarin therapy. [105, 118, 386] Major independent risk factors for bleeding during long-term warfarin therapy have included comorbid conditions other than the indications for therapy, history of stroke, history of GI bleeding, advancing age (greater than 65 years), and the intensity of anticoagulant therapy. [105, 118, 127, 315, 386] Increased variation in the INR is associated with an increased frequency of haemorrhage independent of the mean INR. [116, 117] This effect is probably attributable to increased frequency and degree of marked elevations in the INR.

Bleeding complications with anticoagulant drugs appear to occur more frequently in older patients than in younger individuals. [105, 386-389] Most

individuals who receive oral anticoagulant therapy are elderly patients with AF or VTE. Older patients have characteristics that may place them at higher risk for anticoagulant-related bleeding, but they also have characteristics that make them more likely to benefit from the therapy. [386, 389]

A number of studies have reported that the risk of bleeding associated with warfarin is highest early in the course of therapy. [105, 109, 116, 118-121] In one of these studies, for example, the frequency of major bleeding decreased from 3.0% during the first month of outpatient warfarin therapy to 0.8% per month during the rest of the first year of therapy and to 0.3% per month thereafter. [121]

## 22.2 Reducing anticoagulant adverse events

### 22.2.1 Post-discharge follow-up

As part of the National guidelines from the Australian Pharmaceutical Advisory Council (APAC) for continuum of care, [384] all patients deemed at risk of medication misadventure should be identified and followed-up in the immediate post-discharge period. Medication review allows an assessment of patient adherence and review of medication related problems. A number of problems can occur in the post-discharge phase such as taking the wrong dose, continuing to take medication despite instructions by the physician to discontinue drug therapy, refusal to take a needed medication, continuing to take a medication despite recognised adverse effects or drug interactions known to the patient, and taking another person's medication. [380]

A Cochrane database review examining the effect of expanding the roles of ambulatory pharmacists on patient outcomes and health care use suggests that

pharmacist intervention can improve patient behaviour and adherence and improve physician prescribing. [390]

### 22.2.2 Monitoring anticoagulation intensity

This is covered in more detail in sections 2.1.10.1 and 2.1.10.2. Briefly, the intensity of anticoagulant effect is probably the most important risk factor for ICH, independent of the indication for therapy, with the risk increasing dramatically with an INR > 4.0. [110] The safety and efficacy of warfarin depends on maintaining the INR within the therapeutic range. Analysis of primary prevention trials for stroke prevention in AF, found that a large number of thromboembolic and bleeding events occurred when the INR was outside of the therapeutic range. [110] Analysis of other cohort studies have shown a sharp increase in the risk of bleeding when the INR is higher than the upper limit of the therapeutic range [112-114] and the risk of thromboembolism is increased when the INR falls below 2.0. [38, 111]

### 22.2.3 Patient knowledge and education

Studies have generally shown a relationship between patient knowledge and adverse outcomes of warfarin therapy. [284, 309, 315, 391-395] Good outcomes have been recorded where patients have had increased participation in their care and been encouraged to communicate more effectively with doctors and other health professionals about drug interactions and changes in lifestyle or diet. [327] Compliance with warfarin is essential to maintain good anticoagulant control and to prevent unnecessary dosage changes.[392]

A recent report by Tang et al. [392] evaluated patients' knowledge of warfarin and the relationship to anticoagulant control. Overall, they concluded that patients' warfarin knowledge was poor. Less than 50% of patients knew the strength of their warfarin tablets, the reason for taking warfarin and its effect on the body. They also stated that

> "Their deficiencies in knowledge were even more obvious with respect to the possible consequences of under- or over-anticoagulation, drugs and medicated oils that might interact with warfarin and the management of a missed dose" [392]

Patients who read the anticoagulation booklet on warfarin had better knowledge than those who had not. Most importantly from this study was a positive correlation between patients' warfarin knowledge and the number of INR values that were in the therapeutic range. [392, 395] Pharmacists need to take a key role in reinforcing knowledge regarding anticoagulation to reduce the risk of complications of anticoagulant therapy. Warfarin education needs to be tailored to the level of education and age of the patient. [392] Education of elderly and illiterate patients may require special consideration and include the use of visual aids. [396]

Roddie and Pollock showed that 85% of patients with a good understanding of warfarin had a well controlled and stable INR, compared to only 63% in the poor-understanding group. [396] Generally, patients' knowledge, drug compliance and anticoagulant control all generally improve after patient education became part of a structured management program. [395]

The Newcastle Anticoagulation Study Group found no relationship between knowledge and INR level but found a positive relationship between

education level and knowledge. Importantly they noted "knowledge was generally poor" and 24% of patients answered less than half of the questions correctly. [397]

Functional Health Literacy (FHL) is a measure of a person's ability to perform basic reading and numeric tasks in the healthcare context, such as reading insurance forms and medication labels, and performing mathematical tasks associated with taking medications (numeracy). A body of research exists demonstrating that patients with inadequate FHL have worse health status, problems communicating with healthcare providers, poorer knowledge of their chronic disease state, are at increased risk of hospitalisation, and are more likely to be confused about medications. [397] Inadequate FHL may be a barrier to assessing medication adherence because these patients are more likely to have difficulties accurately reporting to pharmacists the drugs they are currently taking.

A recent study among patients taking warfarin in a pharmacist-run anticoagulation clinic demonstrated that patients with inadequate FHL were less likely than patients with adequate FHL to articulate their weekly warfarin regimen accurately. Of note, providing patients with a simple visual aid (a digitised, color warfarin pill menu from which patients could identify their doses) significantly reduced the FHL-related disparities in warfarin regimen accuracy. [175]

In a study cohort of patients treated with warfarin for stroke prophylaxis in AF, (Figure 29) only 45% of the study cohort believed that there was some risk associated with warfarin therapy in the form of either bleeding or poisoning, whereas the majority of patients (55%) were not aware of any of the specific risks. [175]

**TABLE 3. Patient Perceptions of Warfarin**

| | All Groups | Indo-Asian | Afro-Caribbean | White | *P* Value |
|---|---|---|---|---|---|
| Reasons for commencing warfarin | | | | | |
| Aware of any of the following: heart disease, "thick blood," or risk of stroke | 62 (52%) | 19 (50%) | 14 (50%) | 29 (55%) | |
| Only because "doctor told me to" | 57 (48%) | 20 (50%) | 13 (50%) | 24 (45%) | 0.85 |
| Awareness of warfarin preventing blood clots | | | | | |
| Aware | 79 (66%) | 15 (38%) | 23 (85%) | 41 (77%) | |
| Not aware | 40 (34%) | 24 (72%) | 4 (15%) | 12 (23%) | <0.001 |
| Awareness of warfarin preventing stroke | | | | | |
| Aware | 77 (65%) | 19 (49%) | 16 (59%) | 42 (79%) | |
| Not aware | 42 (35%) | 20 (51%) | 11 (41%) | 11 (21%) | 0.008 |
| Perception of any risk of warfarin treatment | | | | | |
| Not aware | 46 (39%) | 22 (56%) | 8 (30%) | 16 (30%) | |
| Bleeding | 33 (27%) | 7 (18%) | 9 (33%) | 17 (33%) | |
| Poisoning | 21 (18%) | 2 (5%) | 8 (30%) | 11 (20%) | |
| None | 19 (16%) | 8 (21%) | 2 (7%) | 9 (17%) | 0.03 |
| Not aware+None | 65 (55%) | 30 (77%) | 10 (37%) | 25 (47%) | |
| Bleeding+Poison | 54 (45%) | 9 (23%) | 17 (63%) | 28 (53%) | 0.002 |
| General feelings about warfarin therapy | | | | | |
| My doctor has given me enough information about warfarin | 46 (39%) | 12 (30%) | 3 (11%) | 31 (59%) | |
| I am careless at times about taking warfarin | 50 (42%) | 23 (59%) | 18 (68%) | 9 (17%) | |
| Taking warfarin makes me worry about my health | 59 (50%) | 29 (75%) | 24 (90%) | 6 (11%) | |

**Figure 29 Patient perceptions of warfarin.**
Reproduced from Lip et al. [175]

An understanding of how patients feel about warfarin therapy is important, as this may be a potential reason for noncompliance to warfarin therapy. [355] Noncompliant patients have been shown to be more likely to feel that their doctor was not very concerned about them or was less willing to listen to their concerns, but they were less likely to feel that taking warfarin benefited their health, prevented blood clots, or protected their future health. [398]

## 22.3 Project aims and objectives

The overall aim of the final study described in this thesis was to reduce complications associated with anticoagulants in a population of patients commenced on warfarin. The objectives of this study was to implement and evaluate a randomised controlled trial intended to promote the smooth transition of patient care from hospital to the community by incorporating home follow-up

and POC monitoring of patients commenced on warfarin. The following objectives were to be measured comparing the intervention to normal care; the intention was to determine whether the program

- Resulted in safer and more effective initiation of anticoagulation, as measured with a range of outcomes, including the achievement of a therapeutic INR value on day 8 after discharge from hospital, reduced anticoagulant-related bleeds, and less unplanned readmissions related to anticoagulation (thromboembolic or haemorrhagic complications) within 90 days of initial discharge from hospital; and
- Was valued and welcomed by patients and their GPs.

# CHAPTER TWENTY THREE: METHODS

## IMPROVING WARFARIN INITIATION

### 23.1 Recruitment procedure

Patients were recruited from the RHH. As described previously, the RHH is a 450-bed acute care teaching hospital and the only major public hospital in the southern region of Tasmania (serving a population of approximately 230,000). Inpatients initiated on warfarin at the RHH, between February 2002 and June 2003, were prospectively identified by SLJ and/or ward pharmacists. SLJ was not a formal employee of the hospital. Those patients who provided informed consent (Appendix 15) were allocated to either the intervention (Home monitoring: HM) or control (Usual Care: UC) group using a computer-generated random number sequence. Patients were informed to which group they were randomised. All patients received regular medical, nursing and pharmacy care during their hospitalisation.

### 23.2 Home monitoring procedures

GPs for patients in the HM group were telephoned at discharge to inform them that their patient had consented to be involved in the project. HM patients received a home-visit by the project pharmacist on alternate days on 4 occasions, with an initial visit two days after discharge from hospital. The project pharmacist using POC INR monitoring tested the INR (CoaguChek S, Roche Diagnostics, Australia), and discussed a number of important educational points regarding anticoagulant therapy such as goals, adverse effects and interacting medications

with warfarin. The pharmacist used a standard warfarin educational booklet as the basis of the counselling and also developed an A4 warfarin document to assist in education purposes (Appendix 16) The pharmacist liaised with family members and community pharmacists where necessary to ensure follow-up education and support was provided.

Patients' GPs were telephoned with each INR result during the four visits and subsequent dosage changes, if considered necessary, were discussed. All GPs were sent a personalised letter (Appendix 17) and information sheet (Appendix 18) when the patient was discharged, indicating the group that the patients were enrolled to and what follow-up they would receive. GPs assigned to the HM received a personalised letter after the fourth visit containing INR results and doses received during the follow-up (Appendix 19); a GP survey was also sent with this letter with a reply paid envelope.

## 23.3 Usual care group procedures

Instructions in the letter (Appendix 20) to GPs caring for UC patients, indicated that this project was not responsible for the monitoring of their patients and patients would receive a visit from the project pharmacist 8 days after discharge to determine anticoagulant control. GPs caring for UC patients were telephoned on Day 8 if an adverse trend was identified or if the INR was out of the therapeutic range.

## 23.4 Data collection

Baseline demographics, indication for anticoagulation, current medications and presence of contraindications to warfarin (Appendix 21) were assessed after consent for enrolment had been given. The quality of anticoagulation whilst in hospital was also recorded, and assessed against the RHH anticoagulation protocol (Appendix 4) for initiation of warfarin. Adherence to the protocol was defined as giving the appropriate dose for each patient for the first two days of initiation, and was assessed by SLJ.

Alternate day INRs for four visits after discharge were recorded for the HM group; duration of the visits and outcomes were also assessed. The UC group had their INR measured at day 8 post-discharge. The number of pathology tests taken by the GP (patient and/or GP reported) and INR results obtained by the GP (patient and/or GP reported) were also recorded.

A modified multiple-choice 'satisfaction questionnaire' (Appendix 22), based on a similar post discharge project by Naunton et al. [398] was given to each HM group patient, to be completed anonymously after the fourth visit, along with a reply-paid envelope. A systematic step-wise approach to assessing bleeding (major and minor) and embolic complications, adapted from Heidinger et al., [320] was used. All patients were interviewed at 90 days after discharge to assess these complications, the types and frequency of these events. The event rates were assessed through a combination of self-reported events and medical record notes.

Patient knowledge was assessed using a self-administered questionnaire (Appendix 23) with a reply paid envelope by all patients at 90 days after initial discharge using a composite questionnaire from previous studies. [392, 395, 399]

## 23.5 Data analysis

A number of outcomes were assessed, including the achievement of a therapeutic INR value on day 8 after discharge. Therapeutic ranges according to RHH anticoagulation protocols were used. The therapeutic range for AF, VTE, mural thrombus and biological heart valves were 2.0-3.0. The therapeutic range for mechanical heart valve was 2.5-3.5.

Primary outcomes were total, major and minor bleeding complications, and unplanned readmissions due to anticoagulant-related complications. Bleeding was defined as major if it was clinically overt and associated with either a decrease in the haemoglobin level of at least 2g per decilitre or the need for a transfusion of 2 or more units of red cells; if it was retroperitoneal or intracranial; if it warranted the permanent discontinuation of warfarin or if it required hospital admission. All other bleeding complications were assessed as minor.

The medical records of all patients who reported symptoms of embolic complications (TIA, stroke, AMI, complications of DVT) were examined and GPs contacted if necessary to confirm these events. Secondary outcomes were unplanned readmissions from any cause, death (cause determined from death certificates), proportion of patients remaining on anticoagulant therapy and warfarin knowledge assessed 90 days after initial discharge. Follow-up was complete through patient interview and medical record review for all patients.

Rates of outcomes were expressed as number and percent of events with 95% CI. Responses between groups were compared by Mann-Whitney tests and Kruskal-Wallis tests for non-parametric responses. Changes within groups for numerical variables were compared by Wilcoxon-signed rank tests. Categorical variables were compared by $\chi^2$ tests. GPs were anonymously surveyed using a 10-

point Likert scale and HM patients were anonymously surveyed (Appendix 22) after the fourth visit to assess their opinions of the service. The INR values during hospital admission and after discharge were plotted with median and inter-quartile ranges marked at 10, 25, 75 and 90 percentiles. The following colouring was applied to tables to assist in readability of outcomes at discharge, day 8 and day 90 after discharge.

| |
|---|
| Sub-therapeutic |
| Therapeutic |
| Supra-therapeutic |

## 23.6 Exclusions

Exclusions comprised patients who were not being discharged home in Southern Tasmania, who had dementia and were unable to answer basic questions about their therapy or who were entering the Patients Acute Treatment and Care in the Home (PATCH) program. The PATCH program is comparable with hospital in the home treatment programs utilised in other hospitals. Patients are still classed as inpatients of the hospital but are treated at home. Patients who were having warfarin re-initiated after surgery were also excluded. The exclusion criteria were kept to a minimum to allow the data to be relevant to a large proportion of patients who are initiated on warfarin in hospital and discharged to community care.

## 24.7 Cost-effectiveness

Based on previous studies [144, 400] that have indicated approximately 50% of major bleeding complications are GI related, 20% are intracranial in origin and 30% are

classified as other major bleeding, the individual costs for each of these types of bleeds was estimated. Data for estimates of costs was obtained from diagnosis related grouping (DRG) codes from public hospitals in Tasmania for the years 2001-2002. [401] The average cost per admission was estimated at $1757, $4764 & $1917 for GI, intracranial and other related major bleeds respectively. Given these proportions of major bleed subtypes, the overall estimated admission cost of a major bleed was $2405. There is a lack of data examining the outcomes of the costs associated with minor bleeding on warfarin. Therefore, It was assumed that the first minor bleeding episode per patient was followed by a GP's appointment (cost $22.65). It was assumed that 1 patient per 1000 of population are initiated on warfarin per year (data from this study). This however does not include estimates of patients initiated on warfarin from private hospitals or in general practice settings.

## 25.8 Sample size calculation

Based on previous studies showing approximately 30% of patients commenced on warfarin experience a bleeding complication within 3 months [89, 105, 118] and given that the aim of the intervention program was to reduce this figure to below 10%, 72 patients were needed per group (at a power of 80% and $p = 0.05$). Data from the RHH indicated that after a median period of hospitalisation of 8 days for DVT and/or PE, 63% of RHH patients had an INR within the therapeutic range. [402] Assuming that approximately 65% of patients commenced on warfarin have a therapeutic INR on day 8 after discharge from hospital and given that the aim of

the intervention program was to improve this figure to at least 85%, 83 patients were needed per group (at a power of 80% and $p = 0.05$).

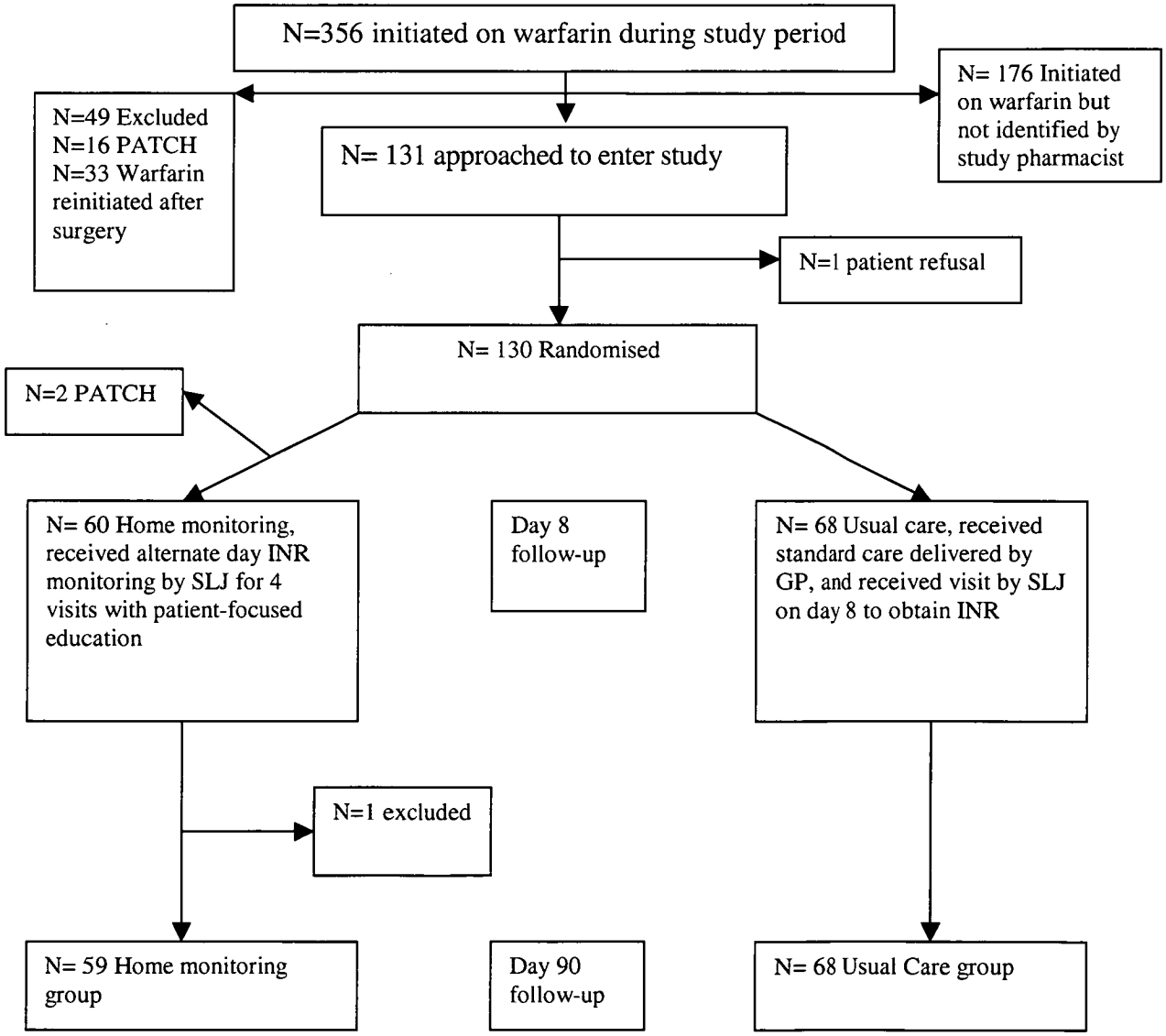
# CHAPTER TWENTY FOUR: RESULTS

## IMPROVING WARFARIN INITIATION

### 24.1 Recruitment

A total of 131 patients were identified as eligible for inclusion. One patient refused participation and two patients enrolled in the HM group were discharged under the care of the PATCH program. Recruitment is displayed in the recruitment flowchart (Figure 30).

**Figure 30 Recruitment flowchart-Improving warfarin initiation**



## 24.2 Characteristics of trial participants

Table 49 summarises the clinical and demographic features of the 128 patients enrolled in the study. The groups were well matched with regard to baseline characteristics. The HM group had a significantly greater number of patients with a previous AMI and trends towards higher amiodarone use at discharge and a history of falls. One patient (HM) was excluded after the day 8 follow-ups, due to the changing of therapy from warfarin to LMWH on advice from the GP on day 8. Therefore, outcomes at 90 days were assessed for 127 patients.

| | Home monitoring n (%) | Usual care n (%) | P value |
|---|---|---|---|
| Participants | 60 (47) | 68 (53) | |
| Age-median (range) | 70 (19-94) | 72.5 (20-91) | 0.93 |
| Age > 75 years | 20 (34) | 27 (40) | 0.50 |
| Female | 28 (47) | 32 (47) | 0.96 |
| Lives alone | 22 (37) | 17 (25) | 0.15 |
| Cognitive deficit | 2 (3) | 4 (6) | 0.5 |
| History of documented falls | 3 (5) | 0 (0) | 0.06 |
| Cardiovascular admission | 39 (65) | 44 (65) | 0.97 |
| History of GI symptoms | 17 (28) | 23 (34) | 0.50 |
| Previous stroke | 7 (12) | 7 (10) | 0.80 |
| Hypertension | 32 (53) | 32 (47) | 0.48 |
| Diabetes | 8 (13) | 13 (19) | 0.38 |
| Previous AMI | 11 (18) | 4 (6) | 0.03 |
| CCF | 13 (22) | 13 (19) | 0.72 |
| Malignancy | 4 (7) | 4 (6) | 0.85 |
| Contra-indications to warfarin | 12 (20) | 7 (10) | 0.12 |
| Previous warfarin use | 8 (13) | 9 (13) | 0.99 |
| Amiodarone use at discharge | 16 (27) | 10 (15) | 0.08 |
| Antibiotic use at discharge | 12 (20) | 19 (28) | 0.32 |
| Interacting drugs at discharge | 48 (80) | 52 (78) | 0.74 |
| Initial bed stay median (range) | 8 (3-72) | 8 (1-65) | 0.47 |
| Comorbidities median (range) | 4 (1-12) | 4 (1-9) | 0.17 |
| Chronic drugs median (range) | 6 (1-12) | 6 (1-15) | 0.59 |
| Interacting drugs median (range) | 1.5 (0-4) | 2 (0-6) | 0.91 |

**Table 49 Baseline characteristics of trial participants**

## 24.3 Indications for anticoagulation

Table 50 describes the reasons for initiation of anticoagulation, with no significant differences between the groups. The most common indication for initiation of warfarin was stroke prevention in AF.

| Reason for use | Home monitoring n (%) | Usual Care n (%) |
|---|---|---|
| AF | 27 (45) | 31 (46) |
| DVT or PE | 19 (32) | 20 (29) |
| Valve replacement | 11 (18) | 12 (18) |
| Mural thrombus | 3 (5) | 5 (7) |

**Table 50 Reason for initiation of warfarin**

## 24.4 Concomitant antithrombotic therapy

Twenty per cent of all patients were prescribed combination antithrombotics, as described in Table 51, with no significant differences or imbalances across the groups.

| Antithrombotics | Home monitoring n (%) | Usual Care n (%) |
|---|---|---|
| Warfarin alone | 50 (83) | 53 (78) |
| Warfarin & aspirin | 9 (15) | 14 (21) |
| Warfarin & clopidogrel | 0 | 1 (1) |
| Warfarin, aspirin & clopidogrel | 1 (2) | 0 |

**Table 51 Antithrombotics on discharge**
(P=0.44 for trends across groups)

## 24.5 Contraindications to anticoagulant therapy

Fifteen per cent of all patients had some contraindication to anticoagulant therapy, according to contraindications listed in the Australian Prescription Products Guide, [104] and identical to those utilised in another study of anticoagulant use at the same institution. [193] There appeared to be a trend towards more contraindications in the HM group compared to UC, but this was not statistically significant. Table 52 summarises actual contraindications to anticoagulant treatment for all patients.

| Contraindication | Home monitoring, n | Usual care, n |
|---|---|---|
| Psychiatric illness | 3 | 1 |
| Falls | 3 | 0 |
| Bleeding tendency | 1 | 2 |
| Blood dyscrasias | 1 | 0 |
| Alcohol abuse | 2 | 0 |
| Poor compliance | 2 | 3 |
| Liver disease | 2 | 0 |
| Malignancy | 1 | 0 |

**Table 52 Contraindications to anticoagulation**
Contraindications total 21, as some patients exhibited more than one.

Table 53 categorises patients according to the bleeding risk index developed by Beyth et al. [127, 386, 389]

| Bleeding Risk | Home monitoring n (%) | Usual care n (%) |
|---|---|---|
| Low | 14 (24) | 17 (25) |
| Medium | 41 (70) | 46 (68) |
| High | 4 (7) | 5 (7) |

**Table 53 Bleeding risk index**
P=0.98 for differences between groups

## 24.6 Quality of anticoagulation at discharge

Table 54 displays the quality of anticoagulation for all patients on discharge from the hospital. There were no significant differences between the groups. The median INR in the HM and UC groups was 2.0 (1.0-3.6) and 2.2 (1.0-4.0), respectively (P = 0.55, U = 1742.5).

| | Home monitoring n (%) | Usual care n (%) |
|---|---|---|
| **Sub-therapeutic** | 29 (49) | 31 (47) |
| **Therapeutic** | 25 (42) | 30 (45) |
| **Supra-therapeutic** | 5 (9) | 5 (8) |

**Table 54 Anticoagulant control at discharge**
P=0.94 for differences between HM and UC groups

Table 55 shows the relationship between bed stay in hospital and quality of anticoagulation at discharge. This implies a longer bed stay for patients who were therapeutic at discharge compared to supra-therapeutic or sub-therapeutic patients. There was, however, no significant difference or imbalance between HM and UC groups.

| | Home monitoring | Usual care | P value |
|---|---|---|---|
| **Sub-therapeutic** | 8 (3-34) | 7 (1-25) | 0.44, U = 397 |
| **Therapeutic** | 10 (6-65) | 10 (4-65) | 0.77, U = 343 |
| **Supra-therapeutic** | 7 (6-30) | 8 (5-12) | 0.92, U = 12.0 |
| **P value** | 0.02, H = 8.19 | 0.01, H = 9.25 | |

**Table 55 Bed stay and INR range at discharge**
Median and range values reported

The median days of warfarin dosing before discharge for the HM and UC groups, 6 days (1-27) and 6 days (1-45), respectively (P=0.66, U=1885). Table 56

illustrates the relationship between number of days of warfarin dosing whilst in hospital and quality of anticoagulation at discharge. The data shows a longer time of warfarin dosing whilst in hospital is closely related to quality of anticoagulation at discharge. There was, however, no difference between HM and UC groups in this respect.

| | Home monitoring | Usual care | P value |
|---|---|---|---|
| **Sub-therapeutic** | 6 (1-13) | 5 (1-21) | 0.51, U = 391 |
| **Therapeutic** | 6 (4-27) | 7 (4-45) | 0.44, U = 315 |
| **Supra-therapeutic** | 7 (5-7) | 5 (3-6) | 0.08, U = 4. |
| **P value** | 0.04, H = 6.3 | 0.002, H = 13.0 | |

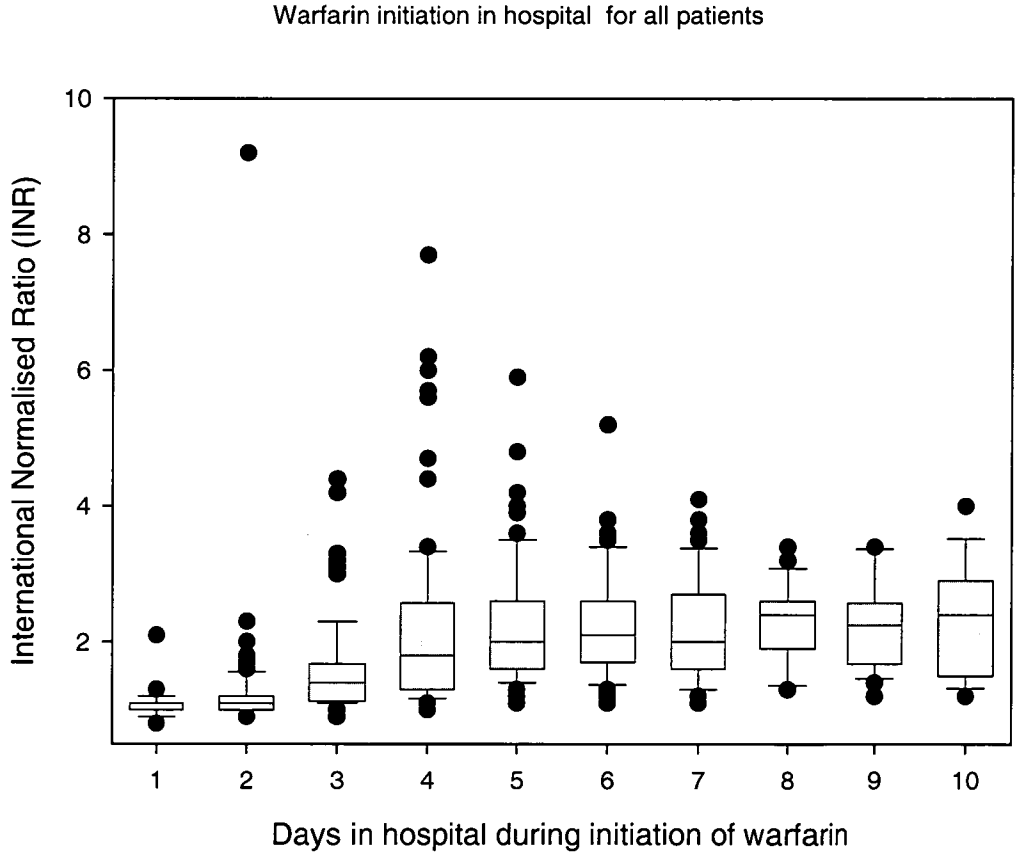
**Table 56 Number of days of warfarin initiation and INR range at discharge.**
Median and range values reported

## 24.7 Quality of warfarin initiation

Figure 31 plots the INR (median and inter-quartile ranges marked at 10, 25, 75 and 90 percentiles) whilst in hospital for all patients, and for the HM and UC groups. A proportion of supra-therapeutic INR values are evident from day 3 after initiation. Figure 32 illustrates warfarin initiation whilst in hospital for the two groups (HM and UC) of patients. Forty-four percent of anticoagulant initiations followed the RHH anticoagulation protocols, 40% in the HM group compared with 47% in the UC group, ($P = 0.43$, $\chi^2 = 0.62$).

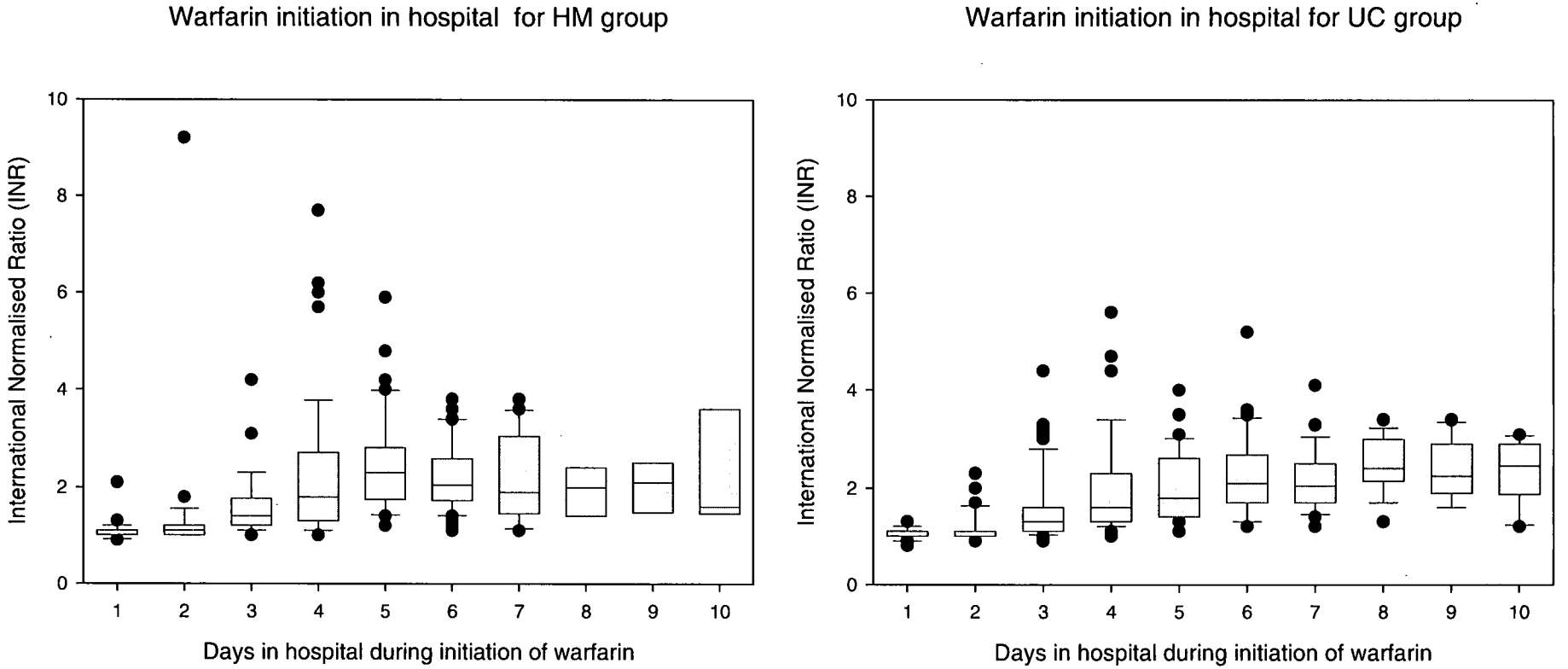
Figure 33 plots warfarin initiation whilst in hospital according to adherence to the anticoagulation protocol. It can be seen that patients who had warfarin initiated according to the anticoagulation protocol had a reduced number of supra-therapeutic INRs compared to when there had been non-adherence to the protocol. For patients whose initiation did not follow the RHH guidelines, 4%, 16% and 10% had INRs greater than 4.0 on days 3, 4 and 5 of their hospital stay,

respectively, compared to none in the guideline-adherent group. The median duration of hospitalisation was one day longer in patients whose warfarin initiation did not follow the RHH guidelines. Eight (6%) patients had a minor bleed whilst in hospital; the INR was 1.0, 1.0, 1.2, 1.6 and 3.9 in five cases and was not ascertainable in three cases. Seven of the eight minor bleeds occurred in patients whose initiation did not follow the protocol, compared to one minor bleed whose initiation followed the protocol ($\chi^2 = 3.5$, $p = 0.06$)




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tests (T) | 107 | 61 | 92 | 96 | 88 | 76 | 45 | 25 | 22 | 15 |
| Patients (P) | 128 | 115 | 111 | 105 | 93 | 82 | 50 | 35 | 27 | 24 |

**Figure 31 INR level in hospital during warfarin initiation**
(T) Number of patients who had INR tests taken on the corresponding day
(P) Number of patients remaining in hospital on the corresponding day

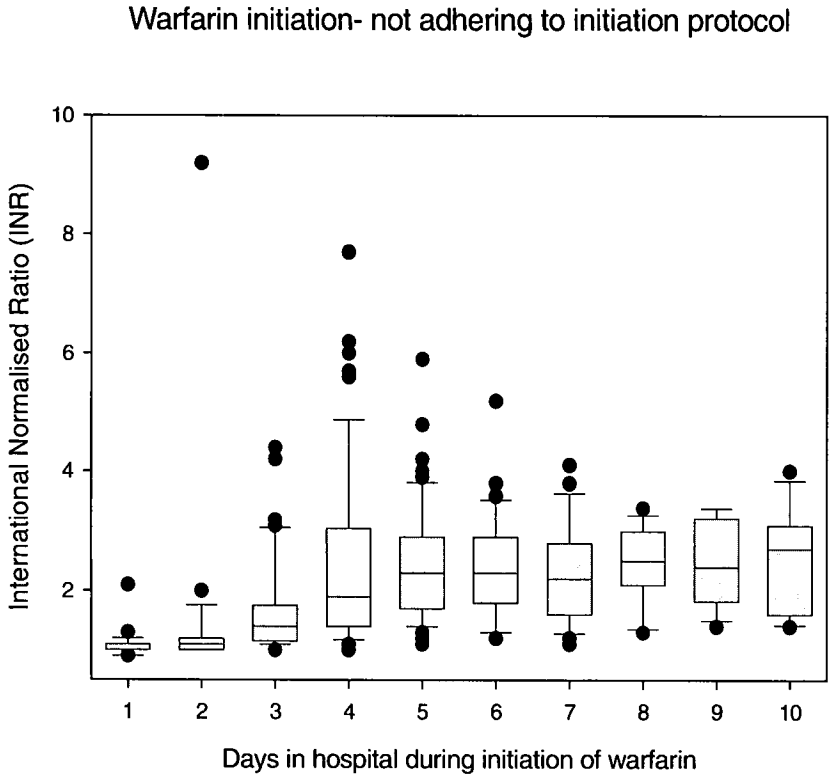


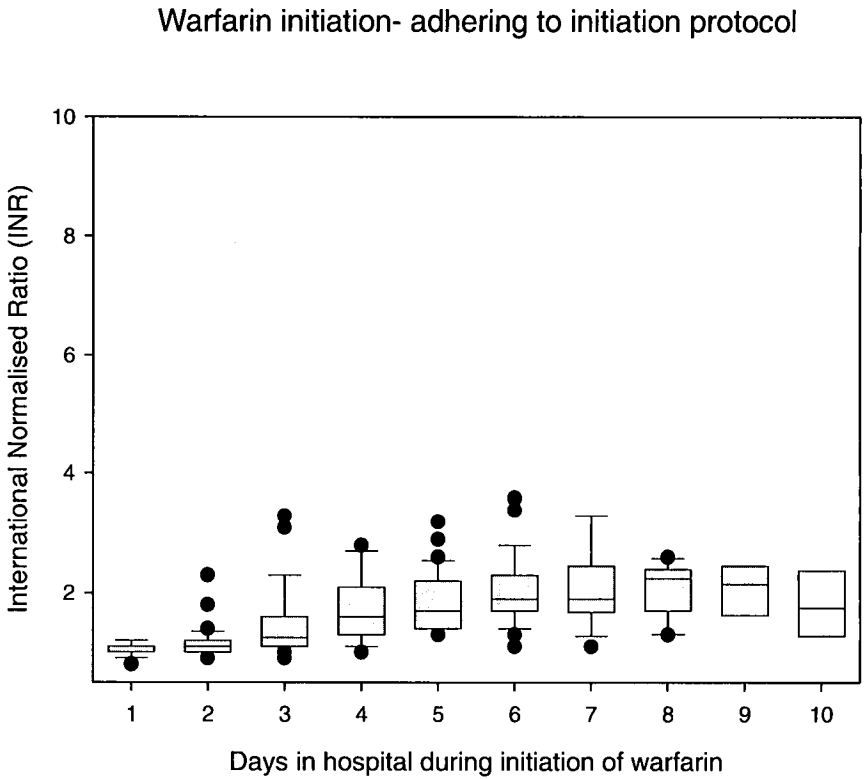

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | 56 | 36 | 52 | 49 | 47 | 36 | 24 | 17 | 14 | 10 | T | 51 | 25 | 40 | 47 | 41 | 40 | 21 | 8 | 8 | 5 |
| P | 68 | 60 | 57 | 53 | 48 | 40 | 26 | 21 | 16 | 14 | P | 60 | 55 | 54 | 52 | 45 | 42 | 24 | 14 | 11 | 10 |

**Figure 32 Warfarin initiation for usual care and home monitoring groups in hospital**

(T) Number of patients who had INR tests taken on the corresponding day

(P) Number of patients remaining in hospital on the corresponding day




| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | 52 | 27 | 53 | 57 | 52 | 45 | 27 | 15 | 14 | 11 | T | 54 | 34 | 39 | 39 | 36 | 31 | 18 | 10 | 8 | 4 |
| P | 71 | 64 | 64 | 62 | 56 | 49 | 32 | 22 | 16 | 14 | P | 57 | 51 | 47 | 43 | 37 | 33 | 18 | 13 | 11 | 10 |

**Figure 33 Warfarin initiation in hospital for initiations not adhering and adhering to anticoagulation protocol.**
(T) Number of patients who had INR tests taken on the corresponding day
(P) Number of patients remaining in hospital on the corresponding day

## 24.8 Anticoagulant control day 8 after discharge

Table 57 displays the level of anticoagulation for all patients at Day 8 after discharge. The median INR in the HM and UC groups was 2.4 (1.3-5.8) and 2.1 (1.0-7.6), respectively (P = 0.84, U = 1602.5).

| | Home monitoring n (%) | Usual care n (%) |
|---|---|---|
| **Sub-therapeutic** | 15 (29) | 21 (33) |
| **Therapeutic** | 35 (67) | 26 (41) |
| **Supra-therapeutic** | 2 (4) | 16 (26) |

**Table 57 Anticoagulant control at Day 8**
P=0.0022 for differences between control and intervention groups

Table 58 Shows a significant trend for UC patients discharged with a sub-therapeutic INR to have a poorer outcome with respect to quality of anticoagulation at day 8 compared with the HM group (P < 0.003). There were no other significant differences between the HM and UC groups with regards to level of anticoagulation at discharge and INR control at day 8. There was no relationship between INR control at discharge and INR at day 8 for the HM group. However, there was a trend towards significance for sub-therapeutic patients in the UC group to have a poorer outcome at day 8 compared to therapeutic and supra-therapeutic patients at discharge in the same group (P = 0.14).

| | Day 8 post discharge INR | | |
|---|---|---|---|
| **Discharge INR** | **Home monitoring n (%)** | **Usual care n (%)** | P value |
| **Sub-therapeutic** | 10 (38) | 8 (26) | 0.003, $\chi^2 = 11.9$ |
| | 16 (62) | 11 (37) | |
| | 0 | 11 (37) | |
| **Therapeutic** | 4 (18) | 10 (37) | 0.30, $\chi^2 = 2.4$ |
| | 16 (73) | 14 (52) | |
| | 2 (9) | 3 (11) | |
| **Supra-therapeutic** | 1 (33) | 3 (60) | 0.38, $\chi^2 = 2.0$ |
| | 2 (67) | 1 (20) | |
| | 0 | 1 (20) | |
| P value | 0.34, $\chi^2 = 4.5$ | 0.14, $\chi^2 = 6.8$ | |

**Table 58 Anticoagulant control at Day 8 by discharge INR range and follow-up type**

| |
|---|
| Sub-therapeutic |
| Therapeutic |
| Supra-therapeutic |

## 24.9 Problems noted in usual care group at day 8

Table 59 displays a brief description of anticoagulant-related problems that were noted at day 8 after discharge in the **UC** group. This list is not exhaustive.

- Mr. JG found to be taking 2.3mg daily at day 8 after discharge. He was confusing his warfarin dose with his INR. His dose was meant to be 2.5mg daily, thus no adverse outcome was reported
- Mrs. PE was discharged on 3mg daily with an INR of 2.0. She had an INR of 1.8 two days after discharge and her GP indicated for her to "alternate 3 and 4mg". Mrs. PE assumes this to mean 3mg in the morning and 4mg at night. Her INR was checked on Day 5 after discharge and an INR of >8 was obtained, this was complicated by the GP not being able to contact Mrs. PE and she took her evening dose of 4mg and 3mg morning dose on day 6. Her warfarin doses were withheld for two days and she was to resume taking warfarin on day 8 at 3mg per day. Her INR was checked by SLJ on day 8 and it was 7.6. The GP was contacted and he suggested withholding the dose for another two days, with Mrs. PE to follow-up with her GP before resuming dosing.
- Mrs. IP aged 88, was discharged on warfarin 5mg daily after receiving two doses in hospital. She continues on 5mg until day 4 after discharge and her INR is 4.8. Warfarin was withheld for two days and her INR at day 6 was 4.0. Warfarin was withheld for another two days and when visited by SLJ at day 8 after discharge her INR was 1.2
- Mrs. MW had received 27mg over 5 days in hospital with a discharge dose of 2mg daily and INR on discharge of 2.6. Her INR on day 3 was 2.0 and she was told to continue on 2mg daily. Her INR when visited by SLJ at day 8 was 1.5; she had received no further testing by her GP.
- Mr. SH was discharged on 3mg daily with INR of 2.9, when in fact he should have been on 1mg daily (communication error between doctor, pharmacist and patient whilst in hospital). His INR on day 3 was 5.0 and Warfarin was withheld for one day, and restarted at 1.5mg daily. His INR when visited by SLJ at day 8 was 1.9; he had received no further testing by his GP.
- Mrs. BR was discharged on 3mg daily with an INR of 3.2. Her INR on day 1 was 3.2 and her dose was reduced to 2mg daily. Her INR on Day 2 was 2.7 and she was told to continue on 2mg daily. Her INR on day 4 was 2.2 and she was told to continue on 2mg daily. Her INR when visited by SLJ at day 8 was 1.4; She had received no further testing by her GP.
- Mr. AF was discharged on 5mg daily with INR of 2.5. His INR on day 2 was 3.9 and the dose was reduced to 4mg daily. His INR on day 4 was 5.5 and warfarin was withheld for one day and resumed at 3mg daily. His INR when visited by SLJ at day 8 was 1.9; he had received no further testing by his GP.
- Mrs. NM was discharged on 6mg daily with an INR of 1.2. Her INR on day 6 was 3.1 and warfarin was withheld. Her INR on day 7 was 2.3 and was withheld again. Her INR when visited by SLJ at day 8 was 1.5.
- Mr. RP was discharged on 2mg daily with INR of 2.2 and whilst in hospital had received 27mg over 6 days. His INR on day 2 was 1.6 and his dose was increased to 2.5mg daily. His INR when visited by SLJ at day 8 was 1.0; he had received no further testing by his

GP.

- Mr. MN was initiated on 5mg of warfarin on the day of discharge. His INR on day 2 was 1.4 and the dose was increased to 7.5mg daily. His INR when visited by SLJ at day 8 was 4.8; he had received no further testing by his GP.
- Mr. AT was discharged with an INR 4.0 on 1mg daily and was instructed to follow-up with his GP on day 3. He saw his GP on day 3 and no INR test was obtained. His INR when visited by SLJ at day 8 was 1.2 and he was still on 1mg. He had received no further testing by his GP.
- Mr. EM was discharged on 1mg daily with INR of 3.8. He was non-compliant with medications and did not present to his GP for INR testing. He indicated to SLJ that he had ceased warfarin on discharge. A pill count indicated he had been taking 1mg daily. His INR on day 8 by SLJ was 5.0.
- Mrs. MS was discharged on 5mg daily with INR of 1.6. She was non-compliant with medication and ceased warfarin on discharge from hospital. Her INR was obtained by her GP on day 7 and the GP was intending to discuss warfarin with the patient. Her INR when visited by SLJ at day 8 was 1.0.
- Mr. RP was discharged with an INR of 2.3 on 4mg daily. His INR on day one was 2.3 and his GP increased his dose to 5mg daily. His INR when visited by SLJ at day 8 was 5.4. He had received no further testing by his GP.
- Mr. RS was discharged with an INR of 1.7 on 5mg daily. His INR on day one was 1.8 and his GP increased his dose to 6mg daily. His INR on day 4 was 3.2 and the dose was reduced to 5mg daily. His INR when visited by SLJ at day 8 was 4.8. He had received no further testing by his GP.

**Table 59 Examples of anticoagulant-related problems noted at day 8 in the UC group**

## 24.10 Anticoagulant control during follow-up

Table 60 displays the level of anticoagulation for the HM group at each visit after discharge, with two-thirds of patients in the HM group having a therapeutic INR at Day 8 after discharge.

| Anticoagulant control | Day 2 n (%) | Day 4 n (%) | Day 6 n (%) | Day 8 n (%) |
|---|---|---|---|---|
| **Sub-therapeutic** | 34 (57) | 25 (42) | 23 (41) | 15 (29) |
| **Therapeutic** | 23 (38) | 24 (40) | 26 (46) | 35 (67) |
| **Supra-therapeutic** | 3 (5) | 11 (18) | 7 (13) | 2 (4) |

**Table 60 Anticoagulant control by day of follow-up**

Figure 34 plots the INR (median and inter-quartile ranges marked at 10, 25, 75 and 90 percentiles) after discharge and day of follow-up in the HM group and Figure 35 shows the INR at discharge and Day 8 in the UC group, with slightly more than one-quarter of patients having a supra-therapeutic INR at Day 8.

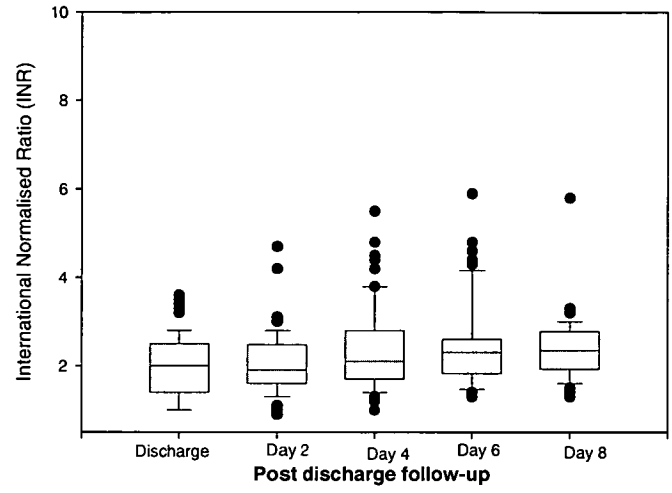



**Figure 34 INR at discharge and at each day of follow-up for the home monitoring group**
Median and inter-quartile ranges marked at 10, 25, 75 and 90 percentiles

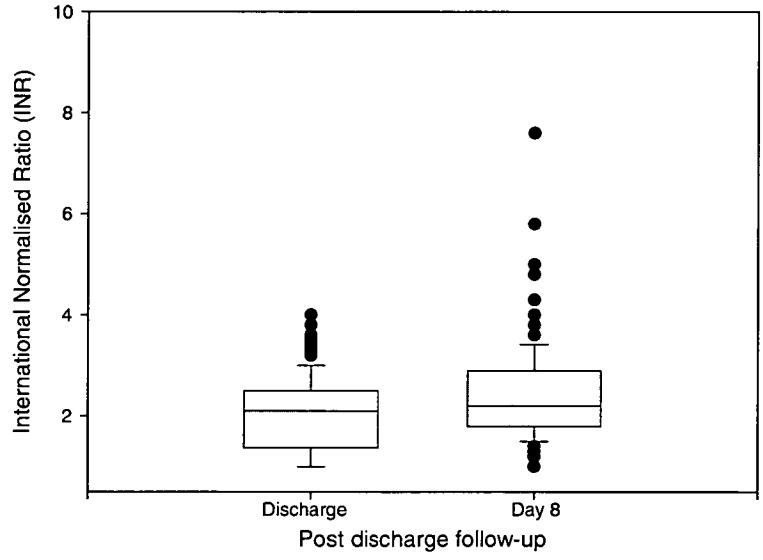



**Figure 35 INR after discharge for the usual care group**
Median and inter-quartile ranges marked at 10, 25, 75 and 90 percentiles

Table 61 displays the median doses for all patients at discharge, day 8 and day 90 after discharge. There was a trend towards a significant difference between

discharge and day 8 doses in the UC group. Table 62 shows that significantly more patients in the UC group compared with the HM group had the same dose at discharge and day 8. Given that the difference in dose between discharge and day 8 approaches statistical significance, it is likely that dose changes that occurred in sixty percent of the UC group were large.

Table 61 shows a highly significant difference between day 90 and day 8 doses in the UC group, and a weakly significant difference in the HM group between day 8 and day 90 doses. This is reinforced in Table 62 that shows significantly more patients in the HM group compared with UC had the same dose at day 8 and day 90.

| | **Home monitoring** | | **Usual care** | | P value |
|---|---|---|---|---|---|
| Discharge | 3 | | 4 | | 0.49, U=1860 |
| Day 8 | 3 | | 3 | | 0.35, U=1470.5 |
| Day 90 | 4 | | 3.5 | | 0.85, U=1264 |
| P value | 0.59*, t = -0.5, df = 51 | 0.03#, t = -2.2, df = 42 | 0.07* t = 1.8, df = 61 | 0.004#, t = -3.0, df = 52 | |

**Table 61 Median dose (mg) for patients at different days of follow-up**
*Denotes difference between discharge dose and Day 8 and # denotes difference between Day 8 and Day 90. (Paired t test)

| | **Home monitoring n (%)** | **Usual care n (%)** | **P value** |
|---|---|---|---|
| Same dose at discharge and day 8 after discharge | 10 (19) | 26 (42) | 0.009, $\chi 2=14$ |
| Same dose at day 8 and day 90 after discharge | 17 (40) | 10 (19) | 0.025, $\chi 2=32$ |

**Table 62 Proportion of patients in each group with the same dose at different times of follow-up**

## 24.11 Duration of home visits

The median duration of pharmacist visits in the intervention group at each visit after discharge are displayed in Table 63. Attempts to contact GPs were made in the majority of cases, but some home visits arose on weekends when GPs were non contactable. If this was reasonably foreseeable, an after hours contact number was obtained or dose adjustment plans were made in advance.

| | Day 2 | Day 4 | Day 6 | Day 8 |
|---|---|---|---|---|
| Patient visit at home | 30 (15-80) | 25 (10-60) | 20 (10-40) | 20 (10-60) |
| Discussion with GP | 1 (0-6) | 1 (0-5) | 1 (0-3) | 1 (0-5) |

**Table 63 Median times taken for home visits in minutes (range)**
The range is 0 in some cases, as the GP was not contactable.

## 24.12 Clinical outcomes at day 8

After the Day 8 visit by the pharmacist to UC patients, 10% had a subsequent dose increase and 13% had a dose decrease. The median number of conventional pathology INR tests was 0 (0-2) in the HM group, and 2 (0-6) in the UC group by day 8 after discharge.

Only 24 patients (37%) of UC patients were using their warfarin booklet to record their INR results compared to 100% of HM patients ($P<0.0001$, $\chi^2 = 55.6$). At 90 days after initial discharge 20 (31%) UC patients compared with 28 (51%) HM patients were using their warfarin books to record INR results ($P=0.02$, $\chi^2 = 4.75$). Table 64 describes each adverse outcome that occurred up to day 8 after discharge.

| Event |
|---|
| **Usual care (n=5)** |
| ▪ Shortness of breath on exertion with a background of PE, INR 3.7 |
| ▪ Angina secondary to AF, INR 1.7 (nil enoxaparin cover) |
| ▪ Tachycardia and confusion after AVR, INR 2.5 |
| ▪ Wound infection, INR 3.8 |
| ▪ Death- (not readmitted)-Myocardial infarction |
| **Home monitoring (n=8)** |
| ▪ Sudden onset of chest pain (unstable angina) INR 2.3 |
| ▪ Stroke, INR 1.8 (anticoagulant cover with enoxaparin 1.5mg/kg) |
| ▪ Pleuritic chest pain (somatisation of acopia) INR 2.0 |
| ▪ Headache for investigation, INR 2.8 |
| ▪ Falls post AVR, INR 7.6 |
| ▪ Death- (not readmitted)-Myocardial infarction |
| ▪ Wound infection after total colectomy, INR 4.6 |
| ▪ Likely recurrent DVT with sub-therapeutic, INR 1.7 (nil enoxaparin cover) |

**Table 64 Description of readmission outcomes by study group occurring up to day 8 after discharge**

## 24.13 Rates of clinical outcomes at 90 days after discharge

Table 65 displays number and rates of adverse events occurring up to 90 days after discharge for all patients (n=127). There was a significant reduction in total bleeding complications (9% vs 24%) between the HM and UC groups. There was also a significant reduction in major and minor bleeding complications between the HM and UC groups, (1% vs 7% for major bleeds and 9% vs 23% for minor bleeds respectively). For patients who were readmitted to hospital during the 90-day follow-up, there were no significant differences in the median readmission INR (the first readmission INR) between the UC and HM groups, 2.6 (1.3-9.9) and 2.6 (1.6-7.6) respectively.

| Outcomes | Home monitoring n (%) [95% CI] | Usual care n (%) [95% CI] | P value |
|---|---|---|---|
| Total bleeding | 9 (15) [7-27] | 24 (35) [24-48] | 0.009, $\chi^2$=6.9 |
| Major bleeding | 1 (2) [0-9] | 7 (10) [4-20] | 0.05, $\chi^2$=4.0 |
| Minor bleeding | 9 (15) [7-27] | 23 (34) [23-46] | 0.01, $\chi^2$=6.0 |
| Embolic complication | 5 (9) [3-19] | 7 (10) [4-20] | 0.73 |
| Unplanned readmission | 13 (22) [12-35] | 18 (27) [17-39] | 0.56 |
| ED* admissions | 8 (14) [6-25] | 13 (19) [11-30] | 0.36 |
| Any unplanned readmission | 19 (32) [21-46] | 27 (40) [28-52] | 0.38 |
| Warfarin ceased prior to 90 days | 12 (20) [11-33] | 15 (22) [13-34] | 0.81 |
| Unplanned cessation | 7 (12) [5-23] | 7 (10) [4-20] | 0.55 |
| Warfarin-related readmission | 2 (3) [0-12] | 5 (7) [2-16] | 0.32 |
| Death | 4 (7) [2-16] | 5 (7) [2-16] | 0.90 |

**Table 65 Adverse outcomes occurring up to 90 Days after discharge**
*Emergency department admissions

## 24.14 Description of clinical outcomes

Table 66 and Table 67 document each major bleeding and embolic complication for all patients. Table 68 describes the cause of death from death certificates for all patients.

| Adverse event |
|---|
| **Usual care (n=7)** |
| ▪ Recurrent haematuria, requiring cessation of warfarin |
| ▪ Massive epistaxis requiring hospital admission, INR 9.9 |
| ▪ Recurrent gastrointestinal bleeding, warfarin ceased, hospitalised & transfused 2 units packed cells, INR on admission 2.6 |
| ▪ (1) Massive epistaxis requiring hospital admission INR 8.3, & (2) Gastrointestinal bleeding for one week INR 7.8 both requiring hospital admission |
| ▪ Severe bruising causing cessation of warfarin by GP |
| ▪ Recurrent haematuria for investigation, INR on admission 2.2 |
| ▪ Gastrointestinal bleeding, requiring hospital admission, four units of packed cells given, INR on admission 4.7 and vitamin K administered |
| **Home monitoring (n=1)** |
| ▪ Recurrent gastrointestinal bleeding, transfused 2 units packed cells, requiring hospital admission |

**Table 66 Description of major bleeding complications occurring up to 90 days after discharge**

| Adverse event |
|---|
| **Usual care (n=7)** |
| ▪ Myocardial Infarction (3)<br>▪ Transient ischaemic attack (2)<br>▪ DCR cancelled due to sub-therapeutic INR and suspected formation of left atrial emboli on echocardiography<br>▪ Admission to hospital with symptoms of embolic complication with sub-therapeutic INR |
| **Home monitoring (n=5)** |
| ▪ Myocardial Infarction (2)<br>▪ Admission to hospital with symptoms of embolic complication with sub-therapeutic INR<br>▪ Unstable angina pectoris<br>▪ Stroke |

**Table 67 Description of embolic complications occurring up to 90 days after discharge**

| Adverse event |
|---|
| **Usual care (n=5)** |
| ▪ Acute myocardial infarction (2)<br>▪ Sepsis with bone marrow suppression and disseminated intravascular coagulation<br>▪ Cardiac arrhythmia on background of congestive cardiac failure and atrial fibrillation<br>▪ Cardiac arrest on background of ischaemic heart disease |
| **Home monitoring (n=5)** |
| ▪ Acute myocardial infarction (2)<br>▪ Thalamic tumour<br>▪ Cerebrovascular accident on background of arteriosclerosis and hypertension |

**Table 68 Description of cause of death from death certificates**

All unplanned cessations of warfarin assessed at 90 days after discharge occurred as a result of death or complications of anticoagulant therapy. There did not appear to be any significant correlations between anticoagulant control at day 8 (supra-, sub- or therapeutic) and subsequent bleeding (total, major or minor) complications for all patients, for the HM group or UC groups. However, 25% (4 events) of the patients in the UC group who had a supra-therapeutic INR at day 8 had a subsequent embolic event during the 90 days after discharge, compared with 1 event each in the sub- and therapeutic patients ($\chi^2 = 5.97$, $p < 0.05$). There was no significant correlation between anticoagulant control at day 8 and embolic outcomes for the HM group.

## 24.15 Anticoagulant control at 90 days after discharge

At 90 Days after discharge, INR measurements were obtained from 100 patients. There was a trend towards more HM patients compared to UC with a therapeutic INR at 90 days after discharge as displayed in Table 69. The median INR for all patients 90 days after discharge was 2.3 (1.0-4.5). The median INR in the HM and UC groups was 2.4 (1.0-3.7) and 2.3 (1.0-4.5), respectively (P = 0.95, U = 1259.0).

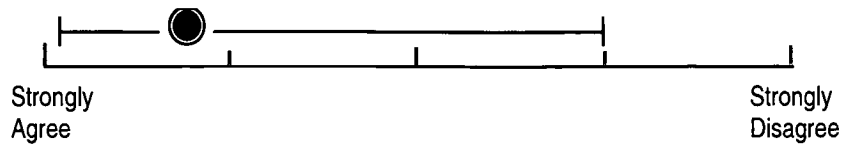
| | **Home monitoring n (%)** | **Usual care n (%)** |
|---|---|---|
| **Sub-therapeutic** | 15 (32) | 19 (35) |
| **Therapeutic** | 29 (62) | 24 (45) |
| **Supra-therapeutic** | 3 (6) | 10 (19) |

**Table 69 Anticoagulant control at 90 days after discharge**
P=0.13, $\chi^2 = 4.1$ for trend across the usual care and home monitoring groups

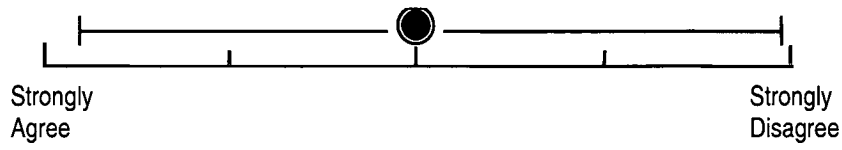
## 24.16 General practitioner survey

Of the 52 GP evaluations sent after the completion of the day 8 protocols, 42 were returned giving a response rate of 81%. The results are shown in Figure 36 and unsolicited comments are displayed in Table 70.

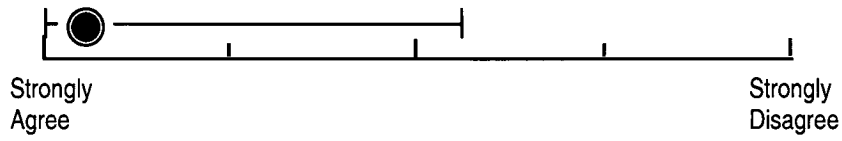
1. I found this to be a valuable service provided to my patient(s).



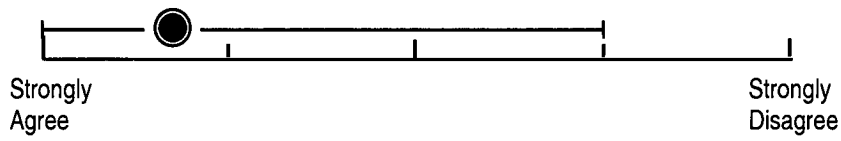

2. I would feel more confident in initiating or managing newly initiated patients on warfarin if this was a regular service.



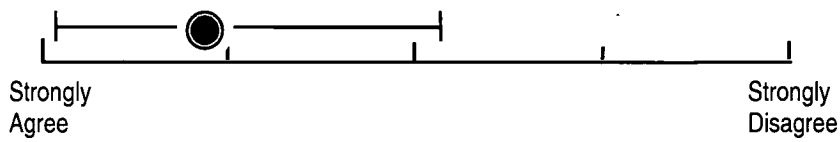

3. I received adequate feedback from the pharmacist.




4. I believe that more patients would benefit from this type of service.




5. I found the suggestions made by the pharmacist to be useful.




6. I believe that my patient(s) found this to be a worthwhile service.

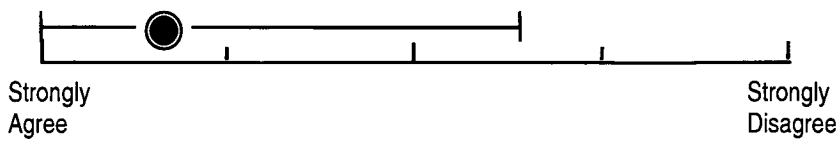



**Figure 36 GP responses to the evaluation questionnaire**

Medians, with range lines plotted at the 10$^{th}$ and 90$^{th}$ percentiles

| |
|---|
| Didn't go for long enough |
| This is a fairly accurate way of measuring INR, hopefully it will be used more in general practice |
| Period of monitoring should vary according to patient. 4 visits still but a difficult patient according to individual circumstances |
| Especially new patients starting but also older patients as the warfarin dose can be confusing |
| Need to compare INR result with that of laboratory |
| I have no trouble doing INRs without a pharmacist but they were very nice |
| Accuracy & cost |
| I feel this service is irrelevant. We have many patients on INRs for many years for varied conditions and feel quite confident in managing them |
| Reliability of the INR test compared to lab testing, if is reliable why aren't GPs allowed to use and claim for these tests in their surgeries, POC testing should be funded by the by the commonwealth under the medicare scheme |
| Shane I have been away from the practice till today, therefore I cant really comment |
| The money involved could provide me with a monitor to more efficiently manage my bourgeoning INR load |
| Improved safety factor for patient |
| I am used to monitoring my own but for elderly it is useful. Is there some reason why GPs could not do the same thing |
| This is like teaching us GPs how to suck eggs |
| How soon can we start and keep up the good work |
| Patient & Dr confidence in dealing with warfarin, especially since patient has had bleeding on warfarin previously. Please keep this service going it is excellent |
| Not sure about accuracy? |
| Better liaison at start, I doubled up with INRs as I didn't know this service was happening |
| Great because in patients home |
| Sorry Shane, but I don't think a pharmacist needs to be involved. The concept of the INR monitor is good though |
| There would be a place for more flexibility e.g. daily INRs I'm happy with the service. In this particular case it seems inappropriate to have commenced the patient on 3mg this meant that the INR as very slow to rise and the INR was far from therapeutic at day 8 |
| This patient required other blood tests during the week and it would be good if somehow that could be coordinated with the home visit for INR |
| Pleased to participate, with thanks |
| It will be very useful for doctor if this service continues |
| LW was scheduled to have an operation ~ 1 week after hospital discharge. Why not use Clexane to tide him over that week then start warfarin after the procedure. Note as well that he had vitamin K in hospital so that his initial INRs are lower than expected |
| Patient was confused when pharmacist output ceased, who was giving instructions? Where was Shane? That nice young man! |

**Table 70 Comments about the monitoring from general practitioners**

## 24.17 Patient satisfaction survey

Of the 52 satisfaction surveys given to the HM patients on completion of the day 8 protocol (8 did not complete the day 8 follow-up), 44 surveys were returned completed giving a response rate of 85%, and the results are shown in Table 71. All of the patients who indicated that they were quite dissatisfied with the contact subsequently indicated that the information they had received helped them a great deal. Unsolicited comments about the anticoagulant monitoring and education are displayed in Table 72.

| Reponses to questions | n (%) |
|---|---|
| *How satisfied are you with the amount of contact you had with the pharmacist?* | |
| Quite dissatisfied | 3 (7) |
| Indifferent or mildly dissatisfied | 0 |
| Mostly satisfied | 0 |
| Very satisfied | 41 (93) |
| *Has the information and other services provided by the pharmacist helped you to deal more effectively with your new medication warfarin?* | |
| Yes, they helped a great deal | 43 (98) |
| Yes, they helped somewhat | 0 |
| No, they didn't really help | 0 |
| No, they seemed to make things worse | 1 (2) |
| *Did you get the kind of information and other services you wanted from the pharmacist?* | |
| No, definitely not | 1 (2) |
| No, not really | 0 |
| Yes, generally | 6 (14) |
| Yes, definitely | 37 (84) |
| *Is there other information you need, or would like, about warfarin and have not received?* | |
| Yes, there definitely is | 3 (7) |
| Yes, I think there is | 3 (7) |
| No, I don't think there is | 26 (61) |
| No, there definitely is not | 11 (26) |
| *Overall, how would you rate the quality of the service that you received from the pharmacist?* | |
| Excellent | 43 (98) |
| Good | 1 (2) |
| Fair | 0 |
| Poor | 0 |
| *Did you find the regular warfarin (INR) monitoring** | |
| Painful | 1 (1) |
| Informative | 21 (30) |
| Motivating | 4 (6) |
| A waste of time | 0 |
| Interesting | 15 (21) |
| Annoying | 0 |
| Too frequent | 0 |
| Beneficial | 29 (42) |
| *Do you think this service would be best provided in your home or at your local pharmacy?* | |
| Home | 38 (88) |
| Local pharmacy | 5 (12) |
| *Do you think this service should be available to all patients commencing warfarin therapy?* | |
| Yes | 41 (100) |
| No | 0 |
| *If this were a regular service would you be prepared to pay for it?* | |
| Yes | 35 (83) |
| No | 7 (17) |
| *If you answered yes to the previous question, how much would you be prepared to pay per visit?* | |
| $1-$5 | 19 (54) |
| $6-$10 | 10 (29) |
| $11-$15 | 5 (14) |
| $16+ | 1 (3) |

**Table 71 Responses to patient satisfaction survey from patients in the intervention group**

Totals are less than 44 for some questions, due to non-completion.

*Totals more than 44 responses as patients could indicate more than one response.

| |
|---|
| My family and I appreciated the courtesy of Mr Jackson at all times. |
| Very punctual & helpful. |
| A thoughtful efficient and friendly service had been provided. |
| A very helpful young man willing to help in any way and I wish him the very best for the future, thank you Shane. |
| Was very pleased with the service provided by Shane Jackson. |
| Definitely available to everybody, I couldn't afford it. |
| As a daughter of the elderly patient on warfarin I found Shanes' help and advice of great benefit to assisting me to help and explain to my mum. Should be an ongoing regular service. |
| Shane is the right person for this type of help as he is most informative with his detail for taking the prescribed dosage. Thank you Shane, God bless you in your life. |
| Mum would like to say she was very satisfied and very grateful for Shanes' service and care also for the extra bits he did with her medication as her family we really appreciated his care and communication, thank you. |
| Friendly, helpful service. Young man very helpful and informative. |
| The treatment I received from the pharmacist Shane Jackson was excellence. |
| Shane Jacksons' visits were very informative and pleasant. |
| This appears to me to be a quite essential service for new patients starting warfarin. If this were to be implemented for all there must be a reduction in complications/failures of warfarin therapy. One needs at least 2-3 sessions with the pharmacist before one feels comfortable with understanding warfarin. |
| Shane Jackson was the most helpful person we have dealt with, ever. |
| I think it is very important that the patient is kept informed of what going on. How to fill the warfarin book and all to see if the correct tablets are taken. Four visits is great benefit to the patient. |
| As my wife does not drive we have appreciated the visits from the pharmacist. |
| Shane very helpful. |
| Reference to question 10, $5.00 per visit for pensioners. |
| Shane done his job very well and answered all the questions we asked and some we did not think of. |
| I found the pharmacist, Shane Jackson very helpful and explained every detail about warfarin clearly. |
| Visits always very friendly and seemed immediately to put you at ease. |
| Warfarin is a good tablet but it has its side effects for me. No more than one I can handle as it upsets me tummie. |

**Table 72 Unsolicited comments from patients**

## 24.18 Patient knowledge questionnaire

Patient knowledge was assessed 90 days after initial discharge, and the responses are shown in Table 73. Fifty-two of 63 eligible patients in the UC group and 33 of 55 eligible patients in the HM group returned the knowledge questionnaire – a response rate of 83% and 60%, respectively ($p = 0.01$ $\chi 2 = 6.3$).

| Responses | | All patients n (%) | Home monitoring n (%) | Usual care n (%) |
|---|---|---|---|---|
| *Since starting warfarin would you say that your general health has* | | | | |
| Improved | P=0.09, $\chi^2$=4.9 | 41 (53) | 21 (68) | 20 (43) |
| Worsened | | 5 (6) | 1 (3) | 4 (9) |
| Stayed the same | | 32 (41) | 9 (29) | 23 (49) |
| *Correct reason for using warfarin* | | | | |
| Yes | P=0.26, $\chi^2$=1.3 | 74 (89) | 31 (94) | 43 (86) |
| No | | 9 (11) | 2 (6) | 7 (14) |
| *Do you worry about warfarin treatment?* | | | | |
| A lot | P=0.86, $\chi^2$=0.3 | 9 (11) | 3 (9) | 6 (12) |
| A little | | 29 (35) | 11 (33) | 18 (36) |
| Not at all | | 45 (54) | 19 (58) | 26 (52) |
| *When you left the Royal Hobart Hospital (RHH) were you handed a "warfarin booklet"?* | | | | |
| Yes | P=0.77, $\chi^2$=0.08 | 79 (93) | 31 (94) | 48 (92) |
| No | | 6 (7) | 2 (6) | 4 (8) |
| Not Sure | | 0 | 0 | 0 |
| *Were you told how warfarin works, and was this clear?* | | | | |
| Yes, and clear | P=0.85, $\chi^2$=0.32 | 64 (79) | 25 (81) | 39 (78) |
| Yes, but not clear | | 13 (16) | 5 (16) | 8 (16) |
| No | | 4 (5) | 1 (3) | 3 (6) |
| *Could you briefly explain in your own words how warfarin works* | | | | |
| Thins the blood | P=0.35, $\chi^2$=2.1 | 50 (59) | 20 (61) | 30 (58) |
| Prevents clots | | 16 (19) | 8 (24) | 8 (15) |
| No written response | | 19 (22) | 5 (15) | 14 (27) |
| *Were you told of the possible problems with warfarin treatment, and was this clear?* | | | | |
| Yes, and clear | P=0.36, $\chi^2$=2.0 | 61 (73) | 26 (81) | 35 (67) |
| Yes, but not clear | | 18 (21) | 5 (16) | 13 (25) |
| No | | 5 (6) | 1 (3) | 4 (8) |
| *Were you told what to do if you have a nosebleed or bruising and was this clear?* | | | | |
| Yes, and clear | P=0.01, $\chi^2$=8.7 | 58 (69) | 28 (85) | 30 (59) |
| Yes, but not clear | | 15 (18) | 1 (3) | 14 (28) |
| No | | 11 (13) | 4 (12) | 7 (14) |

| Responses | | All patients n (%) | Home monitoring n (%) | Usual care n (%) |
|---|---|---|---|---|
| *Were you told what drugs to avoid and was this clear?* | | | | |
| Yes, and clear | P=0.06, $\chi^2$=5.7 | 49 (60) | 23 (77) | 26 (50) |
| Yes, but not clear | | 17 (21) | 4 (13) | 13 (25) |
| No | | 16 (20) | 3 (10) | 13 (25) |
| *Were you given advice on drinking alcohol and was this clear to you?* | | | | |
| Yes, and clear | P=0.003, $\chi^2$=11.9 | 66 (83) | 33 (100) | 33 (70) |
| Yes, but not clear | | 6 (8) | 0 | 6 (13) |
| No | | 8 (10) | 0 | 8 (17) |
| *Could starting a new treatment or any other preparation affect your warfarin treatment?* | | | | |
| Yes | P=0.23, $\chi^2$=3.0 | 48 (58) | 22 (69) | 26 (51) |
| No | | 6 (7) | 1 (3) | 5 (10) |
| Don't know | | 29 (35) | 9 (28) | 20 (40) |
| *The following are statements about any patient drinking alcohol while receiving warfarin treatment* | | | | |
| *Alcohol can affect anticoagulant treatment* | | | | |
| Yes | P=0.09, $\chi^2$=2.9 | 56 (82) | 24 (92) | 32 (76) |
| No | | 12 (18) | 2 (8) | 10 (24) |
| *Alcohol must be totally avoided* | | | | |
| Yes | P=0.70, $\chi^2$=0.15 | 21 (31) | 7 (28) | 14 (33) |
| No | | 47 (69) | 18 (72) | 29 (67) |
| *8 units of alcohol a night is OK (for example 8 glasses of beer or wine)* | | | | |
| Yes | P=0.63, $\chi^2$=0.24 | 4 (6) | 1 (4) | 3 (7) |
| No | | 62 (94) | 23 (96) | 39 (93) |
| *1 unit of alcohol a night is OK (for example 1 glass of beer or wine)* | | | | |
| Yes | P=0.60, $\chi^2$=0.28 | 54 (79) | 19 (76) | 35 (81) |
| No | | 14 (21) | 6 (24) | 8 (19) |

| Responses | | All patients n (%) | Home monitoring n (%) | Usual care n (%) |
|---|---|---|---|---|
| *Of the list below indicate which of the following could interfere with your warfarin therapy?** | | | | |
| Aspirin | P=0.77, $\chi^2$=0.09 | 67 (80) | 25 (78) | 42 (81) |
| Weather conditions | P=0.89, $\chi^2$=0.03 | 3 (4) | 1 (3) | 2 (4) |
| Coffee | P=0.55, $\chi^2$=0.35 | 13 (16) | 4 (13) | 9 (17) |
| Herbal Remedies | P=0.34, $\chi^2$=0.93 | 39 (46) | 17 (53) | 22 (42) |
| Panadol | P=0.25, $\chi^2$=1.4 | 18 (21) | 9 (28) | 9 (17) |
| Some illnesses | P=0.30, $\chi^2$=1.1 | 36 (43) | 16 (50) | 20 (39) |
| Missed dose of warfarin | P=0.08, $\chi^2$=3.1 | 56 (67) | 25 (78) | 31 (60) |
| Nurofen | P=0.37, $\chi^2$=0.79 | 23 (27) | 7 (22) | 16 (31) |
| Antacids | P=0.16, $\chi^2$=1.9 | 23 (27) | 6 (19) | 17 (33) |
| Some foods | P=0.47, $\chi^2$=0.52 | 51 (61) | 21 (66) | 30 (58) |
| *Of the list below, which of the following could be side effects of taking the wrong (too little or too much) warfarin?** | | | | |
| Blood in stools | P=0.34, $\chi^2$=0.91 | 48 (58) | 20 (65) | 28 (54) |
| Nausea | P=0.59, $\chi^2$=0.29 | 13 (16) | 4 (13) | 9 (17) |
| Blood in the urine | P=0.93, $\chi^2$=0.008 | 45 (54) | 17 (55) | 28 (54) |
| Nervousness | P=0.02, $\chi^2$=5.2 | 3 (4) | 3 (10) | 0 |
| Blood clots | P=0.62, $\chi^2$=0.25 | 47 (56) | 19 (59) | 28 (54) |
| High blood pressure | P=0.61, $\chi^2$=0.27 | 16 (19) | 7 (22) | 9 (17) |
| Weakness | P=0.32, $\chi^2$=1.0 | 14 (17) | 7 (22) | 7 (14) |
| Ringing in the ears | P=0.47, $\chi^2$=0.53 | 8 (10) | 4 (13) | 4 (8) |
| Nose bleeds | P=0.22, $\chi^2$=1.5 | 62 (74) | 26 (81) | 36 (69) |
| Sleeplessness | P=0.93, $\chi^2$=0.01 | 5 (6) | 2 (6) | 3 (6) |
| Prolonged bleeding after cuts | P=0.23, $\chi^2$=1.4 | 68 (81) | 28 (88) | 40 (77) |
| Bruising without injury | P=0.16, $\chi^2$=1.9 | 61 (73) | 26 (81) | 35 (67) |
| Loss of appetite | P=0.55, $\chi^2$=0.35 | 13 (16) | 4 (13) | 9 (17) |

**Table 73 Patient knowledge 90 days after discharge**

Statistics comparing HM and UC groups

Responses do not total 85 in all cases as some patients did not answer all questions

*Proportion of patients responding "YES" to each question

## 24.19 Cost-effectiveness

The money saved in healthcare related costs by instituting this intervention across the country would amount to nearly $Aust4 million dollars per annum in reduced bleeding costs as displayed in Table 74. From data obtained in this study, it is estimated that approximately 20,000 patients are initiated on warfarin in hospital per annum.

| Cost savings of home monitoring compared with usual care | |
|---|---|
| No. Patients initiated on warfarin per annum | 20000 |
| Major bleed in the first three months of warfarin treatment (n) UC-10% | 2000 |
| Major bleed in the first three months of warfarin treatment (n) HM-2% | 400 |
| Major bleeds "saved" from instituting HM (first three months of treatment) | 1600 |
| *Costs saved from major bleeds per annum (000s) ($) | 3848 |
| Minor bleed in the first three months of warfarin treatment (n) UC-34% | 6800 |
| Minor bleed in the first three months of warfarin treatment (%) HM-15% | 3000 |
| Minor bleeds "saved" from instituting HM (first three months of treatment) | 3800 |
| Costs saved from minor bleeds per annum (000s) ($) | 86 |
| Total costs saved per annum (000s) ($) | 3934 |

**Table 74 Cost savings associated with home monitoring compared with usual care**

*Average major bleeding costs were estimated to be $2405, sourced from DRG codes from public hospitals in Tasmania for the years 2001-2002. (Section 24.7)

The approximate time spent with the patient over the course of the intervention neared two hours in total. The approximate traveling time for this type of intervention is likely to be similar, therefore, the total time costs would approximate 4 hours, likely to be paid at $40 per hour (total time costs of $160) Additional costs such as test strips, lancets, telephone calls and travel costs would likely bring costs in the order of approximately $200 per patient. The program would cost approximately $Aust4 million for 20,000 patients per annum. It is

therefore likely that this program is cost neutral if the costs of bleeding are solely compared with the costs of the program. However, these estimates do not take into account general practice or private hospital initiation of warfarin.

Performing a sensitivity analysis, if the difference in major bleeding risk was reduced to 8% from 10% in the UC group, the program would save $Aust 2.9 million, thus bringing the cost-effectiveness of this program into question.

# CHAPTER TWENTY FIVE: DISCUSSION

## IMPROVING WARFARIN INITIATION

This study examined the effect of POC monitoring of anticoagulant therapy, with patient-focused education by a pharmacist, amongst a population of newly initiated warfarin patients who were discharged from hospital to GP care. This study has clearly shown that control of anticoagulation after discharge from hospital is sub-optimal, with some patients at high-risk of anticoagulant-related complications because of lack of appropriate testing and dosing. We found that this comprehensive program reduced the frequency of bleeding in patients randomly assigned to HM at the start of anticoagulant therapy.

The majority of the study population represented those chronically ill older patients, who were initiated on warfarin for the treatment of chronic conditions. The two groups were well matched in baseline characteristics, except for a significantly higher incidence of previous AMI in the HM group. We are unaware of any lifestyle differences between the two groups that could have been responsible for this difference. However, if a number of baseline demographics are reported the risk of random chance contributing to a significant difference in these variables increases.

The study population represents those patients who are at high risk of anticoagulant misadventure if not adequately monitored and educated. Elderly patients are at an increased risk of bleeding complications but are also have a higher benefit with anticoagulant therapy compared to younger populations. [386, 389] In fact nearly half of the patients had warfarin initiated for stroke prophylaxis in AF.

There is clear evidence that the trend to early discharge for hospital patients is putting strain on the primary care system. This study, which commenced in 2002, has shown that 44% of all patients had a therapeutic INR at discharge, compared to 63% in a previous audit of anticoagulant therapy at the same hospital, completed in 1994. [402] The median days of initiation of warfarin in the previous study was 8 days compared to 6 in this study. We have shown that a longer time in hospital generally means a longer time of warfarin initiation, and this is correlated with the likelihood of having a therapeutic INR at discharge.

This study shows the actual practice of initiation of warfarin in a teaching hospital and subsequent discharge of patients to community care may result in poor outcomes, compared with follow-up after discharge. The combination of shorter periods of hospitalisation and increasing usage of warfarin is placing stress on general practice health services to care for newly anticoagulated patients.

This project meets a number of the principles of the APAC national guidelines to achieve the continuum of quality use of medicines between hospital and community. [384] It appears that standard care for discharge of newly initiated anticoagulated patients is not fulfilling key roles of the national guidelines.

> "It is the responsibility of the admitting institution to ensure the development and coordination of a medication discharge plan for each patient"
>
> "Information to the patient's health care providers should include details of the medication management during the hospital stay..... And any specific needs with respect to drug management"

Fifteen per cent of all patients had some contraindication to anticoagulant therapy. This reflects clinical practice initiation of warfarin where relative

contraindications to warfarin exist, which may increase the risk of bleeding in this group of patients. It is inevitable that warfarin may be used in some patients who have a relative contra-indication to its use, but the benefit of warfarin may outweigh the risk of bleeding in some cases. For example, the mortality rate from an untreated pulmonary embolism approaches 30% [93] and the risk of bleeding in patients who have relative contraindications to warfarin have not been accurately quantified.

Twenty per cent of all patients were prescribed combination antithrombotics reflecting current trends for anticoagulant and antiplatelet therapy in combination for some conditions. [1, 403-405] This, however, leaves patients at a higher risk of bleeding complications. [403, 406, 407] A high proportion (80%) of patients were discharged on medication that could interact with warfarin. This is higher than a study by Howard et al. [408] reporting 54% of AF patients aged over 65 years were prescribed concomitant medications that could interact with warfarin. As the number of interacting medications with warfarin increases, so does the risk of fluctuations in the INR [73, 76, 408-410] and potentially the risk of bleeding.

Less than adequate initiation of warfarin may have caused problems after discharge in both groups of patients. Despite the availability of initiation protocols in the hospital, the initiation of warfarin continues to be a problem. The anticoagulant effect of any daily dose of warfarin in the initiation phase is generally seen after two days; [74] therefore poor initiation of anticoagulation whilst in hospital may have an impact on post-discharge INRs. The initiation of warfarin in hospital and adherence to RHH anticoagulation protocols appears to be well matched between the two groups of patients, therefore it is unlikely that

differences in warfarin initiation between the UC and HM groups are responsible for different outcomes at day 8 after discharge.

It is disappointing to find that only 44% of warfarin initiations followed the RHH anticoagulation protocols. There was clear evidence showing a number of supra-therapeutic INR after day 3 of initiation in hospital, continuing in some cases through to discharge. Only slightly more than half of patients who were still in hospital on the second day of initiation had an INR ordered. This may have contributed to some high INRs seen after day 3 of initiation whilst in hospital.

The HM group had two-thirds of patients in the therapeutic range at day 8, which had increased from 42% at discharge. Conversely, the proportion of patients in the UC group with therapeutic INR at day 8 was less than the proportion therapeutic at discharge, (41% and 45% respectively). The alarming part of the follow-up at day 8 in the UC group was the high proportion of supra-therapeutic INR. Slightly more than one-quarter of patients in the UC group had a supra-therapeutic INR, and the risk of bleeding in this group of patients is elevated with increasing INR. It is evident that follow-up conducted in the HM group increased the proportion of therapeutic patients at day 8 compared to discharge and also reduced the supra-therapeutic INR that occurred in the UC group.

A similar proportion of patients in both groups were sub-therapeutic at discharge and at day 8, suggesting that the follow-up conducted by the pharmacist is most beneficial at reducing preventable elevations in the INR. It also appears that supra-therapeutic INR at day 8 occur most frequently in patients with sub-therapeutic INR at discharge, reinforcing the benefit of regular monitoring of patients who are not therapeutic or stable.

A proportion of patients in the HM group had supra-therapeutic INR prior to having a therapeutic INR at day 8. This, however, reiterates that initiation doses whilst in hospital may have negative impacts on all patients after discharge. The HM group INR at day 8 confirms that stabilisation of the INR occurred earlier than the UC group. Further evidence pointing to a more stable INR and dose in the HM group is verified by the dose-difference between day 8 and 90 between the two groups. The dose difference in the UC group ($P < 0.01$) was highly significant and the dose difference in the HM group just reached statistical significance ($P < 0.05$). This suggests a number of patients in the UC group had a large difference between their day 8 and day 90 dose, reflecting lack of long-term stability between day 8 and day 90.

An important finding is that only 20% of patients in the HM group were maintained on the same dose at day 8 that they were discharged on. This suggests that some adjusting of doses is necessary post-discharge in most patients. Importantly, 40% of patients in the HM group had the same dose at day 8 and day 90 compared with 20% of UC patients, reflecting superior long-term stability of the INR at day 8. This also indicates that patients in the HM group at day 8 were more likely to have reached their maintenance dose compared to patients in the UC group

At 90 days after discharge there was a larger proportion of patients in the HM group who had a therapeutic INR compared to the UC group, 62% compared with 46%, respectively. This, however, was not statistically significant. Still alarmingly, however, nearly one-fifth of patients in the UC group had a supra-therapeutic INR.

A number of anecdotal cases point to similar root causes of unstable INR after discharge. These cases indicate a lack of sufficient communication between the hospital and GPs, and GPs extending the interval of monitoring too early, and/or increasing dosages too quickly. The study clearly implicates the trend to early discharge as a potential cause for poor communication and outcomes in the usual care group within the study. It is well documented in the literature that many patients have a poorly planned discharge and the GP is not fully informed of their patient's admission or discharge. [411-414]

This project is an example of a systems solution to improve the management of anticoagulation, which looks to improve the processes of care rather than individual behaviour. When processes of care are examined, a common root cause of medication errors occurs at the time when decisions about therapy are made. [415, 416] Failure to obtain sufficient information about the patient or about the pharmaceutical agent has contributed to medication errors. [417] This intervention aimed to provide patients and GPs with information regarding dose decisions at the POC, and has shown an improvement compared to usual care.

A number of systems could be implemented to adhere to the APAC guidelines for continuity of care between hospital and the community for warfarin initiation. These systems include this type of program, improving transfer of information regarding warfarin doses and INR whilst in hospital to the GP, and the utilisation of existing services such as Home Medicines Review (HMR) to improve patient knowledge of anticoagulant therapy. Pharmacists should take a key role in reinforcing knowledge regarding anticoagulation to reduce the risk of complications of anticoagulant therapy.

The impact that the pharmacist had on the UC group at day 8 is difficult to measure, with almost one quarter of the UC group having a dose change after the visit on day 8. It is likely that the visit by the project pharmacist on day 8 may have prevented some type of adverse event in some of the patients visited and, although this is speculative, it is highly likely and difficult to quantify. Data for anticoagulant control between day 8 and day 90 after discharge was unable to be obtained for patients. Therefore, the contribution of the HM to anticoagulant control between these time intervals was unable to be assessed. However, a higher proportion of patients in the UC group with a supra-therapeutic INR at day 8 subsequently developed embolic complications assessed at 90 days after discharge. This may have reflected poor control at day 8 as a marker for erratic control up to 90 days after discharge, potentially contributing to an increased risk of embolic complications.

This study showed a reduction in all bleeding complications in the HM group compared to UC. It is likely a combination of improved monitoring post discharge and education resulted in better outcomes compared to usual care. Total bleeding was reduced in the HM group compared to UC, 15% and 36%, respectively. Importantly, major bleeding was reduced in the HM group compared to UC, 2% compared to 10% respectively. This has significant impact on costs associated with warfarin, and also doctors' perception of anticoagulant therapy.

Despite low rates of warfarin-related bleeding reported in randomised trials, [140-143, 145] which included strict exclusion criteria, higher rates of major bleeding have been reported in many studies of warfarin used in clinical practice. [116, 400, 418] In this study, the sample of patients was assembled with few exclusion criteria, and the bleeding rates in the UC group were similar to those

observed in other clinical practice studies. The intervention achieved a frequency of major bleeding that was similar to the lower rates achieved in previous randomised trials assessing the efficacy of warfarin.

Hylek et al. [419] studied a group of patients in an anticoagulation clinic who obtained an INR greater than 6.0. Nearly 10% of these patients sought medical attention for abnormal bleeding and 5% of these experienced a major haemorrhage within 14 days follow-up. Interestingly, they noted that none of the patients had clinically important bleeding at the time of the INR measurement. This raises the issue that fluctuations in the INR need to be kept to a minimum to reduce the potential for life-threatening bleeding complications.

A study by Beyth et al. [315] evaluated an intervention that consisted of patient education about warfarin, training to increase patient participation, self-monitoring of INR, and guideline-based management of warfarin dosing compared to normal care for six months. The cumulative incidence of major bleeding in the usual care group was similar to our study, 12% and the incidence of major bleeding was reduced to 5.6% in the intervention group. Importantly, they noted that after 6 months, major bleeding occurred with similar frequencies in the intervention and usual care groups.

GP evaluations were generally positive, and they could see the benefit of providing this type of service for patients newly initiated on warfarin. They saw this program as a valuable service to patients, they also thought that more patients could benefit, and that their patients individually benefited from the program. From the evaluation questionnaire it appears that this service has mixed effects in regards to feeling more confident in initiating warfarin, and perhaps this reflects the difficulty of initiation of warfarin, irrespective of type of follow-up.

The pharmacist home visits were well received by patients, and they were very positive in their feedback and evaluation of the service. Most patients found it informative, beneficial and interesting. Over 80% of patients indicated that they would be willing to pay, with most indicating in the range of $1-$5 or $6-10 per visit. It must be acknowledged that most of the group was elderly and receiving social security benefits, which makes the willingness to pay more significant.

Nowadays, it is not enough to show that programs reduce hospital admissions or composite endpoints, we must show that programs are cost-effective or at least cost-neutral. This program was estimated to save nearly $Aust4 million dollars per annum in direct hospital costs if rolled out across the country for patients commenced on warfarin in the hospital setting. The program costs associated with this are likely to add up to a similar figure, and the program would be cost neutral. The cost-neutral assessment of this study is likely a worse case scenario with a larger study likely to show a reduction in other healthcare related expenditure such as VTE and reduced doctors visits from medication related problems.

The low cost associated with bleeding complications (average cost $2405 for a hospital admission) makes the impact of this program appear to be less significant. Given that most of these patients were elderly the likely reduction in healthcare expenditure would be greater than estimated. This type of program needs to be integrated into existing structures to lower the program costs associated with it, thus making it more cost effective. A model with accredited pharmacists conducting testing would have ongoing sustainability after initial training. Previous studies illustrate the potential health and economic benefits of

organised care management approaches and POC monitors in the management of patients receiving warfarin therapy. [420]

Although the generalisability and cost-effectiveness of this program remain to be demonstrated, these findings support the premise that efforts to reduce the likelihood of major bleeding will lead to safe and effective use of warfarin therapy in older patients.

> "Many major improvements in medication use among older adults will also depend on closing the gap between knowledge and practice and increasing the ability of older adults to manage their medications." [376]

In terms of monitoring, some of the best evidence for improvements in primary care relate to the monitoring of warfarin. [282, 284, 421-423] The evidence suggests that nurse led monitoring clinics, [422] computerised decision support systems, [421, 422] patient education and involvement, [284] may help improve control through improved monitoring. In terms of patient adherence, a number of studies have shown that improved education [424] and approaches that provide greater involvement of patients in decision making [424, 425] improve patient adherence and may reduce drug related admissions.

> "Interventions focused on improving patient adherence with prescribed regimens and monitoring of prescribed medications also may be beneficial." [380]

It is difficult to attribute the reduced bleeding complications in the HM group, to any single part of the intervention. The study was not designed to determine the relative importance of the components of the intervention. It is likely that the combination of improved monitoring post-discharge and a patient-focused education program has resulted in a reduction in the number of bleeding complications. It has been reported by a number of studies that adherence to

anticoagulant treatment is enhanced by knowledge and understanding of the drug, its benefits and side effects. [309, 355, 426] In a large observational study investigating reasons for drug related admissions, they were mainly attributed to problems with prescribing, monitoring and patient adherence. [427] The APAC guidelines again refer to follow-up education of patients after discharge

> "Factors influencing the patients' knowledge about the medication and the ability to comply with medication regimens should be identified.....Implementation of drug therapy should be accompanied by the use of appropriate education programs" [384]

The patient-focused education program employed in this project significantly improved knowledge in some areas, and there were clear trends to improved knowledge in other areas. It is possible that components of increased knowledge were responsible for reduced bleeding complications. There may be some non-response sample bias associated with the knowledge assessment, as significantly more patients in the UC group returned their knowledge questionnaire. However, over 60% of patients in the HM group returned the survey, therefore this may be unlikely to have caused a significant difference.

Roddie and Pollock [396] showed that 85% of patients with a good understanding of warfarin had a well controlled and stable INR, compared to only 63% in the poor-understanding group. Generally, patient's knowledge, drug compliance and anticoagulant control all improve after patient education became part of a structured management program. [315, 327, 396, 428] The Newcastle Anticoagulation Study Group [395] found no relationship between knowledge and INR level, but found a positive relationship between education level and knowledge. Importantly, they noted "knowledge was generally poor" and 24% of patients answered less than half of the questions correctly. The questionnaire

utilised in this thesis, incorporated questions used by the Newcastle Anticoagulation study group, and also assessed if patients understood the information given to them.

The knowledge evaluation is limited by its reliance on a questionnaire-based survey. A reason for lower knowledge in the UC group could be due to poor counseling and information giving by health professionals. With regards to written material, Estrada et al. found that some of the patient information on anticoagulant therapy was above the comprehension level of most patients. [429] More emphasis should be given to adequate education of patients on anticoagulant treatment post-discharge, with special emphasis on high-risk groups of patients, such as the elderly and poly-pharmacy users. Warfarin education should be tailored to the level of education and age of the patient. [392, 395] Education of elderly and illiterate patients may require special consideration and include the use of visual aids. [392]

There are some limitations to this randomised controlled trial. We were able to enrol a total of only 128 subjects after exclusions during the timeframe of this study; therefore the actual power was less than intended. The smaller than expected sample size prevented us from attributing any statistical significance to a number of secondary outcomes such as anticoagulant-related readmissions and improved overall anticoagulant knowledge. These preliminary results should be confirmed in larger multi-centre studies.

The trial was non-blinded to allocation concealment and outcome assessment. Allocation concealment would have been difficult to conduct in this type of project. The use of objective criteria for assessment of outcomes at 8 and

90 days, and strict criteria for major bleeding assessment, minimises the risk of blinding status exerting a major influence on trial findings.

The true effect of the intervention may have been understated because patients in the UC group could have been more likely to take an active interest in their anticoagulant treatment due to the Hawthorne effect, which may have underestimated the effect of the intervention. The potential for underestimation of effect is very likely because of the impact the pharmacist had on the UC group when they were seen at day 8 after discharge. Almost one-quarter of patients in the UC group required dose changes as a result of the visit at day 8. It is therefore very likely that the intervention also had a positive impact on the UC group and may have prevented subsequent bleeds that may have occurred if patients' GPs were not contacted at day 8 after discharge and dose changes instituted.

# PART FIVE: CONCLUSIONS

## CHAPTER TWENTY-SIX: GENERAL DISCUSSION

The body of work covered in this thesis gives examples and solutions to address the adverse events associated with anticoagulants. A pertinent quote from Gurwitz states that "The drug itself is not the problem; the problem relates to how the medication is used" [430] and this has large implications surrounding the quality use of anticoagulants. It is important to recall that adverse events comprise under-use, over-use and mis-use. The works described in this thesis are examples of organisational and professional changes that can be made to the current structure and delivery of healthcare, which is likely to reduce anticoagulant-related misadventure. Figure 37 diagrammatically represents the level at which each of the interventions aimed to improve the quality use of anticoagulants. The interventions described were aimed at three broad areas that influence the quality use of anticoagulants: the patient, physician and the healthcare system.

Under-utilisation of antithrombotics for stroke prevention in AF is a major healthcare problem, which may have taken a backseat to patient safety related issues. As stated by Woolf, [213] "people are less likely to die of an overdose of warfarin than of not receiving warfarin at all". He goes on to state "the attention policy makers give to safety should be coupled with a proportionately larger effort to deal with defects in healthcare that affect more lives".

The first two studies described in this thesis, suggest one method of increasing the use of antithrombotics for stroke prevention in AF. The "diagnostic analysis" of barriers to the prescribing antithrombotics for AF enabled the development of an educational program targeting the perceived barriers to

antithrombotics. This program firstly assessed the physician-related factors that influence the under-use of anticoagulants for AF and then aimed to overcome these factors to improve the use of anticoagulants. The education program utilised audit and feedback data, and aimed to clarify any misperceptions that were identified in the nationwide survey.

It was found that, disseminating guidelines followed by the process of academic detailing, significantly increased the prescription of anticoagulants for AF. However, further interventions such as this one needs to be undertaken to influence prescribing at a professional and organisational (system) level.

A number of studies have focused on the need to implement evidence from clinical trials to practice, and we have had a distinct lack of success in closing the gap between clinical trials and clinical practice. As stated by Lenfant "regardless of the reasons cited for this phenomenon — structural, economic, or motivational — the result is the same: we are not reaping the full public health benefits of our investment in research".[431]

It was identified by the responding doctors to the survey investigating barriers to the prescribing of warfarin, that the availability of POC INR monitors might increase their prescribing of warfarin for AF, and improve the management of already anticoagulated patients. There had been no previously published research investigating the use of POC INR monitors in the Australian setting.

Four projects using POC INR monitoring were described in this thesis. Firstly, the accuracy and clinical usefulness of the monitors was established in two settings, an outpatient anticoagulant clinic and a number of rural general practices. The monitors perfomed accurately and the use of these monitors in general practice would appear to be on the horizon. [432]The variation encountered

between the monitor and the laboratory was found to be no more than variation that would be encountered between laboratories. The general practice evaluation provided a potential system change in the way warfarin is montored in the community setting. The availability of portable INR monitors was also suggested by physicians to be a factor influencing the use of anticoagulants for AF.

The third project involving the POC INR monitoring, was based in rural community pharmacies. The pharmacy-based testing provided a new model for anticoagulant management in the community setting, influencing anticoagulant management at a system, patient (through education) and physician level. There is significant evidence that pharmacists are able to assist GPs in the management of chronic diseases, and management of anticoagulation seemed an area that GPs may have needed some assistance. This project concluded that INR monitoring in community pharmacy was feasible and was well received by GPs, patients and pharmacists. The POC monitors performed accurately, and importantly, potentially adverse outcomes were avoided as a result of the pharmacy-based testing. Appropriate training programs need to be developed, to ensure that pharmacy-based testing meets basic requirements for quality assurance and improves clinical outcomes.

The final project described in this thesis, incorporated home-based POC testing and patient-focused education, and resulted in improved outcomes compared to standard care for patients initiated on warfarin in hospital and transferred to GP care. This program influences the quality use of anticoagulants at the three levels specified in the figure: system changes (transfer of information from hospital to GPs and regular monitoring), physician (improved confidence and outcomes with management) and patient (improved knowledge). The

program significantly reduced the incidence of all bleeding complications compared to usual care, and should ideally become incorporated into standard discharge planning for patients initiated on warfarin and discharged to GP care.

There is a large potential for alternative models of anticoagulation management in the community setting that require further research and investigation. Community pharmacy-based clinics, General-practice based anticoagulation clinics and patient self-monitoring or management are possible solutions to the improved management of patients on anticoagulant treatment.

The work described in this thesis was multifaceted in its attempt to influence the quality use of anticoagulants. The different projects conducted were complementary to one another and were successful in improving the outcomes of anticoagulation.

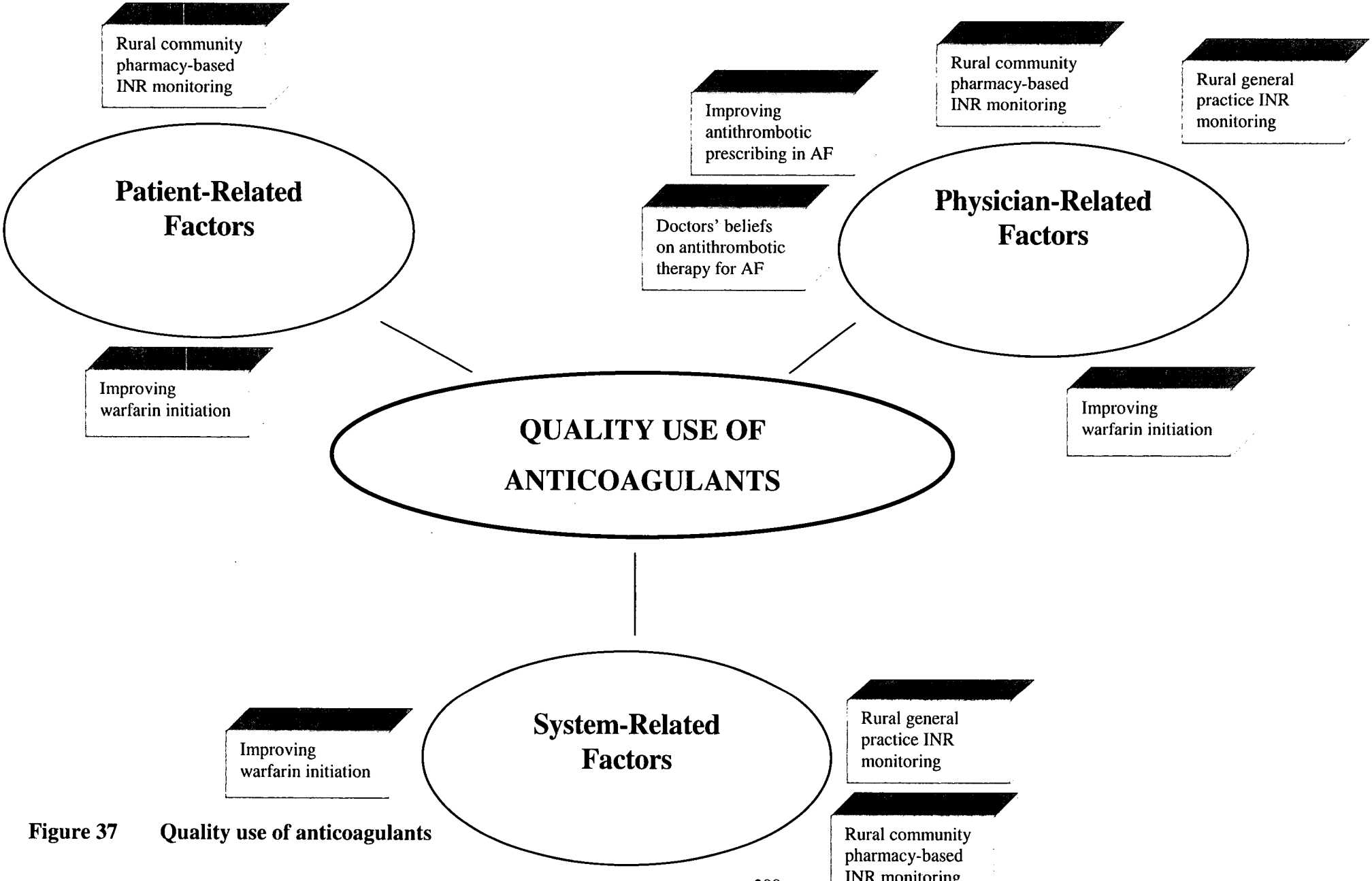



**Figure 37** **Quality use of anticoagulants**

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# APPENDICES

# Appendix 1

## Covering letter to doctors

## Doctors' beliefs on antithrombotic therapy for AF

UNIVERSITY OF TASMANIA

*Tasmanian School of Pharmacy*

*Telephone: 6226 2203*

4 August 2000

Dear Doctor

We are conducting ongoing clinical research into the use and outcomes of thrombosis prophylaxis in atrial fibrillation (AF)[1]. To date, we have established a database of over 500 patients with AF in Southern Tasmania who have presented to the Royal Hobart Hospital. These patients are being followed for embolic and bleeding outcomes related to use of thrombosis prophylaxis. The principal intention is to compare the results of recent clinical trials with outcomes in the real world, and ultimately improve stroke prevention in patients with AF.

We now wish to extend this research by collecting doctors' perceptions on the appropriate use and barriers to antithrombotic therapy in AF.

Your name has been randomly selected from the Medical Directory of Australia 2000 (Australasian Medical Publishing Co). We ask you to participate in this survey by completing the enclosed four page questionnaire. Most questions simply involve responding via ticking a box or placing a cross on a scale. We appreciate your honest opinions. Responses will be treated anonymously and confidentially. Data from all responses will be pooled.

Your assistance is highly valued. The information will assist in developing systems for the provision of safer and more effective antithrombotic therapy.

The study has been approved by both the Research and Ethics Committees, Royal Hobart Hospital.

If you have any questions about the project you can contact either:
Greg Peterson (phone 03-62262197 or email G.Peterson@utas.edu.au) or
Janet Vial (phone 03-62264842 or email Janet.Vial@utas.edu.au).

Please return the completed questionnaire in the self-addressed envelope by 8 September 2000.

We look forward to your response. Thank you for your assistance.

Yours sincerely

Gregory Peterson
**Associate Professor**
**School of Pharmacy**

Janet Vial
**Senior Lecturer/Physician**
**Discipline of Medicine**

[1] Ang SY, Peterson GM, Friesen WT, Vial JH.
Review of antithrombotic drug usage in atrial fibrillation. J Clin Pharm Ther 1998; 23: 97-106

# Appendix 2

## Survey form

## Doctors' beliefs on antithrombotic therapy for AF

UNIVERSITY OF TASMANIA

# *Survey of medical practitioners examining the issue of atrial fibrillation and antithrombotic therapy*

*We appreciate your honest opinions.*
*The responses will be treated anonymously and confidentially, and data from all respondents will be pooled.*

**The first set of questions relates to demographic and practice information.**

1 In which year did you first register as a medical practitioner? 19_____

2 Gender? ☐ Female ☐ Male

3 Which of the following best describes your regular medical practice?

☐ General practitioner ☐ Cardiologist
☐ General physician ☐ Other_____

4 In which **State or Territory** do you normally practice?

☐ NSW ☐ QLD ☐ VIC
☐ SA ☐ TAS ☐ ACT
☐ WA ☐ NT

5 Which of the following best describes the **location** of your regular medical practice?

☐ City ☐ Rural
☐ Suburban ☐ Other_____

6 On average, how many **hours each week** do you **spend seeing patients**?

_____

7 Which of the following best describes the **demographics of your patients**?

☐ Predominantly young patients
☐ Mix of young and older patients
☐ Predominantly older patients
☐ Other _____

8 Approximately **how many new cases with chronic/paroxysmal AF would you see per year**?

_____

**The remaining questions relates to doctors' views on AF and the use of antithrombotic drugs.**

9 **For the following hypothetical patients who have chronic non-valvular AF, indicate what you perceive their annual risk of ischaemic stroke may be and indicate which treatment you feel would be appropriate. Also indicate the target INR you would aim for if using warfarin.**

**a) 65 year old male with a history of thrombo-embolic stroke secondary to AF**

**RISK OF STROKE**

☐ LOW (annual risk of stroke = 1%)
☐ MEDIUM (annual risk of stroke = 4%)
☐ HIGH (annual risk of stroke = 8-12%)

| **DRUG THERAPY** | **TARGET INR** |
|---|---|
| ☐ WARFARIN | INR ____ |
| ☐ ASPIRIN | |
| ☐ ASPIRIN & WARFARIN | INR ____ |
| ☐ NEITHER | |
| ☐ OTHER _____ | |

**b) 75 year old male with a history of thrombo-embolic stroke secondary to AF**

**RISK OF STROKE**

☐ LOW (annual risk of stroke = 1%)
☐ MEDIUM (annual risk of stroke = 4%)
☐ HIGH (annual risk of stroke = 8-12%)

| **DRUG THERAPY** | **TARGET INR** |
|---|---|
| ☐ WARFARIN | INR ____ |
| ☐ ASPIRIN | |
| ☐ ASPIRIN & WARFARIN | INR ____ |
| ☐ NEITHER | |
| ☐ OTHER _____ | |

c) **76 year old female with diabetes, hypertension and a previous AMI 10 years ago**

**RISK OF STROKE**

☐ LOW (annual risk of stroke = 1%)

☐ MEDIUM (annual risk of stroke = 4%)

☐ HIGH (annual risk of stroke = 8-12%)

| **DRUG THERAPY** | **TARGET INR** |
|---|---|
| ☐ WARFARIN | INR ____ |
| ☐ ASPIRIN | |
| ☐ ASPIRIN & WARFARIN | INR ____ |
| ☐ NEITHER | |
| ☐ OTHER _____ | |

d) **45 year old male with hypertension, diabetes, ischaemic heart disease and a past history of TIAs**

**RISK OF STROKE**

☐ LOW (annual risk of stroke = 1%)

☐ MEDIUM (annual risk of stroke = 4%)

☐ HIGH (annual risk of stroke = 8-12%)

| **DRUG THERAPY** | **TARGET INR** |
|---|---|
| ☐ WARFARIN | INR ____ |
| ☐ ASPIRIN | |
| ☐ ASPIRIN & WARFARIN | INR ____ |
| ☐ NEITHER | |
| ☐ OTHER _____ | |

e) **60 year old female with no contributory risk factors**

**RISK OF STROKE**

☐ LOW (annual risk of stroke = 1%)

☐ MEDIUM (annual risk of stroke = 4%)

☐ HIGH (annual risk of stroke = 8-12%)

| **DRUG THERAPY** | **TARGET INR** |
|---|---|
| ☐ WARFARIN | INR ____ |
| ☐ ASPIRIN | |
| ☐ ASPIRIN & WARFARIN | INR ____ |
| ☐ NEITHER | |
| ☐ OTHER _____ | |

f) **50 year old male with hypertension and ischaemic heart disease and a resolved past history of gastrointestinal bleeding**

**RISK OF STROKE**

☐ LOW (annual risk of stroke = 1%)

☐ MEDIUM (annual risk of stroke = 4%)

☐ HIGH (annual risk of stroke = 8-12%)

| **DRUG THERAPY** | **TARGET INR** |
|---|---|
| ☐ WARFARIN | INR ____ |
| ☐ ASPIRIN | |
| ☐ ASPIRIN & WARFARIN | INR ____ |
| ☐ NEITHER | |
| ☐ OTHER _____ | |

**10** Do you believe that the **risk of stroke from paroxysmal AF** is:

☐ Less than for chronic AF

☐ Greater than for chronic AF

☐ Same as for chronic AF

**11** **Warfarin reduces the risk of stroke** in chronic AF by approximately:

☐ 20% ☐ 50% ☐ 66% ☐ 85%

**12** **Aspirin reduces the risk of stroke** in chronic AF by approximately:

☐ 20% ☐ 50% ☐ 66% ☐ 85%

**13** **The annual risk of major bleeding** (ie intracranial or intracerebral haemorrhage, or requiring blood transfusion) in patients with chronic AF treated with warfarin is approximately:

☐ 1% ☐ 5% ☐ 10% ☐ 20%

**14** We are interested in identifying variables that doctors perceive as being barriers to the use of anticoagulation in AF. In a patient with chronic AF, which of the following **factors would make you reluctant to use warfarin**? Answer each by placing a cross anywhere on the scale provided.

**a) bad experiences with prescribing warfarin in the past**

*No, not at all* — *Yes, most definitely*

**b) advancing age of the patient**

*No, not at all* — *Yes, most definitely*

**c) active gastrointestinal bleeding**

*No, not at all* — *Yes, most definitely*

**d) prior resolved gastrointestinal bleeding**

*No, not at all* — *Yes, most definitely*

**e) previous intracranial haemorrhage**

*No, not at all* — *Yes, most definitely*

**f) poor control of INR in the past**

*No, not at all* — *Yes, most definitely*

**g) a history of daily falls**

*No, not at all* — *Yes, most definitely*

**h) a history of twice-yearly falls**

*No, not at all* — *Yes, most definitely*

**i) dementia, but in an institutionalised setting**

*No, not at all* — *Yes, most definitely*

**j) alcoholism**

*No, not at all* — *Yes, most definitely*

**k) liver disease**

*No, not at all* — *Yes, most definitely*

**l) severe anaemia**

*No, not at all* — *Yes, most definitely*

**m) poorly controlled hypertension**

*No, not at all* — *Yes, most definitely*

**n) concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs)**

*No, not at all* — *Yes, most definitely*

**o) patient living distant from routine medical care**

*No, not at all* — *Yes, most definitely*

**15** Do you believe there are clear guidelines that you can refer to if unsure of whether to anticoagulate patients with AF?

*No, not at all* — *Yes, most definitely*

**16** Do you believe that the results given in large clinical trials can be translated into Australian clinical practice?

*No, not at all* — *Yes, most definitely*

**17** Do you believe that most patients with chronic AF would accept treatment with warfarin?

*No, not at all* — *Yes, most definitely*

**18** Do you believe that anticoagulation should be initiated in the hospital setting in patients with AF?

*No, not at all* — *Yes, most definitely*

**19** Do you believe that anticoagulation is underutilised in patients with AF?

*No, not at all* — *Yes, most definitely*

**20** In general, do you believe that the risk of haemorrhage with warfarin outweighs the potential benefit in stroke prevention in patients with AF?

*No, not at all* — *Yes, most definitely*

**21** In general, do you believe that anticoagulation treatment has a negative impact on quality of life in patients with AF?

*No, not at all* — *Yes, most definitely*

**22** Do you believe that most patients with AF find the need for close monitoring while receiving treatment with warfarin too inconvenient?

*No, not at all* — *Yes, most definitely*

**23** If portable INR monitors were made available to your practice would this assist with the management of your patients with AF?

*No, not at all* — *Yes, most definitely*

**24** Do you have any further comments or suggestions on the issue of AF and the use of antithrombotic therapy? Please use the space below.

*Thank you for your time and assistance*

**Please return this questionnaire in the enclosed reply-paid envelope**

# Appendix 3

## Reminder letter to doctors

## Doctors' beliefs on antithrombotic therapy for AF

UNIVERSITY OF TASMANIA

*Tasmanian School of Pharmacy*

*Telephone: 6226 2203*

23 August 2000

Dear Doctor

Just a reminder about our survey of doctors' perceptions on the appropriate use and barriers to antithrombotic therapy in AF.

An explanatory letter and survey form, with reply-paid envelope, were sent to you about two weeks ago. We are grateful if you have completed and returned the survey. If you have not completed the questionnaire yet, your assistance would be highly valued. The information will assist in developing systems for the provision of safer and more effective antithrombotic therapy.

Most questions simply involve responding via ticking a box or placing a cross on a scale. Responses will be treated anonymously and confidentially. Data from all responses will be pooled.

If you need another copy of the questionnaire and envelope, or have any questions about the project you can contact either:

Greg Peterson (phone 03-62262197 or email G.Peterson@utas.edu.au) or
Janet Vial (phone 03-62264842 or email Janet.Vial@utas.edu.au).

Thank you for your assistance.

Yours sincerely

Gregory Peterson
**Associate Professor**
**School of Pharmacy**

Janet Vial
**Senior Lecturer/Physician**
**Discipline of Medicine**

# Appendix 4

# Royal Hobart Hospital

# anticoagulation guidelines

**Attached in sleeve of thesis**

# Appendix 5

## Covering letter to doctors

## Improving antithrombotic prescribing in AF

25 February 2002

UNIVERSITY OF TASMANIA

*Tasmanian Schools of Pharmacy & Medicine*

*Telephone: 6226 2203*

Dear Dr (Doctors name inserted here)

**REDUCING THE RISK OF STROKE IN ATRIAL FIBRILLATION**

We are members of the Tasmanian Schools of Pharmacy and Medicine, Faculty of Health Science at the University of Tasmania and are embarking on a project to assist in providing a clinical approach to reducing the risk of stroke in chronic or paroxysmal non-valvular Atrial Fibrillation.

Chronic AF is the most common arrhythmia in the community with a prevalence rising with age such that it is present in over 10% of the general population over 80 years, and is the most important risk factor for stroke in that age group. The presence of AF has been confirmed in many studies as an important risk factor for ischaemic stroke and other thromboembolic events. The absolute annual risk of stroke in patients with AF of all causes is around 5%, but varies with age and other risk factors.

We recently reviewed the medical records for 505 consecutive patients who had chronic or paroxysmal AF at the Royal Hobart Hospital, and followed these patients to determine clinical outcomes.[1] Analysis of the use of antithrombotic drugs in the patients indicated that a large proportion was not taking appropriate therapy.

- 79% of the patients with previously diagnosed chronic or paroxysmal AF had a high risk of developing stroke at the time of admission to hospital care.
- Only one-third (34%) of these patients were receiving warfarin (or warfarin plus aspirin), with almost one-quarter (24%) receiving no antithrombotic agent.
- Of the high-risk patients without any contraindications, only 43% were receiving warfarin (or warfarin plus aspirin) on hospital admission.
- At follow-up, the annual overall stroke rate for warfarin-treated patients was significantly lower than for patients who did not receive warfarin (3.4% to 7.0% per annum, respectively; $P < 0.05$), a risk reduction for stroke with warfarin therapy of 51%.
- For patients who had no contraindications to the use of warfarin, the rates of major bleeds while receiving warfarin and not receiving warfarin were 2.1% and 1.5% per annum, respectively.

We ask that you read and consider the enclosed information. The guidelines are based on recently published research papers and reviews on the prevention of stroke from AF, and similar guidelines from the UK and USA. The guidelines have been formulated in consultation with local Haematologists, Cardiologists and Geriatricians.

Our project pharmacist, Shane Jackson, will be in contact with you shortly to arrange a convenient time to visit and briefly discuss the material with you. Any queries can be directed to Shane (phone: 0408 485 430). This project has been approved by the Research and Ethics Committees of the Southern Tasmanian Acute Care Program.

Yours sincerely

Shane Jackson
**Project Pharmacist/PhD student**
**TASMANIAN SCHOOL OF PHARMACY**

Gregory Peterson
**Professor of Pharmacy**
**TASMANIAN SCHOOL OF PHARMACY**

Janet Vial
**Physician & Head of Clinical School**
**ROYAL HOBART HOSPITAL**

David Jupe
**Haematologist**
**ROYAL HOBART HOSPITAL**

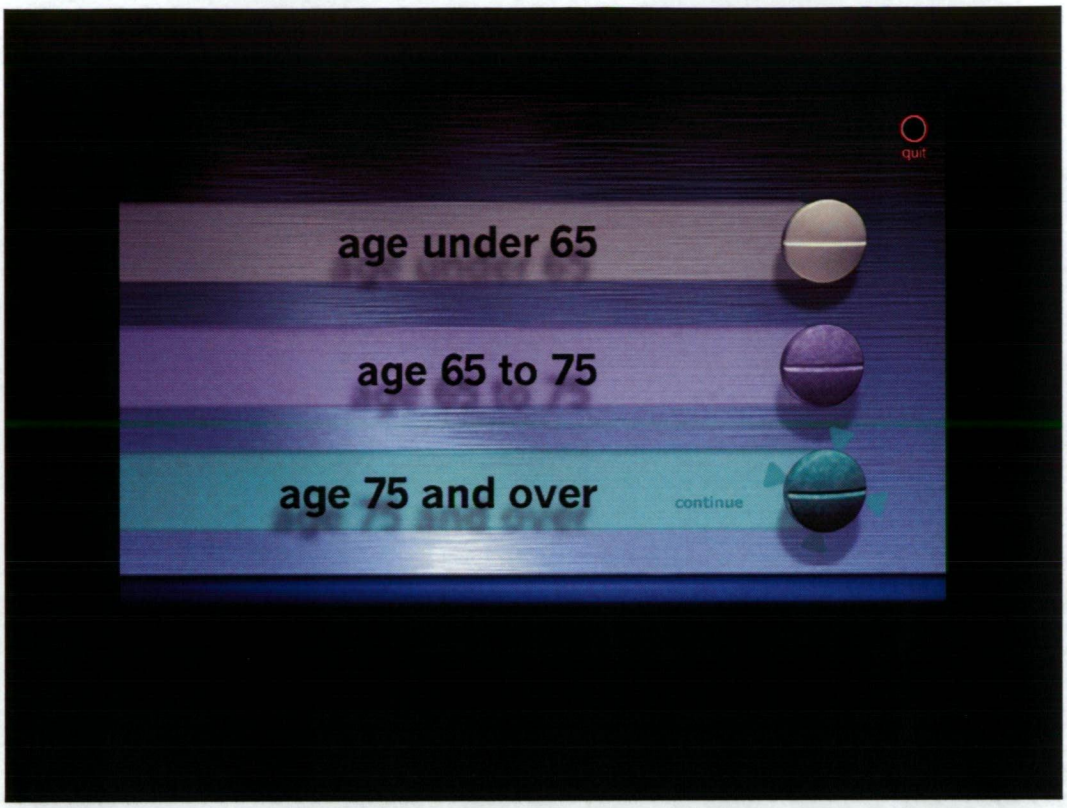
Phil Roberts-Thomson
**Associate Professor/Cardiologist**
**ROYAL HOBART HOSPITAL**

1 Jackson SL, Peterson GM, Vial JH, et al. Outcomes in the management of Atrial Fibrillation: Clinical trial results can apply in practice *Intern Med J* 31 (6): 329-336 AUG 2001

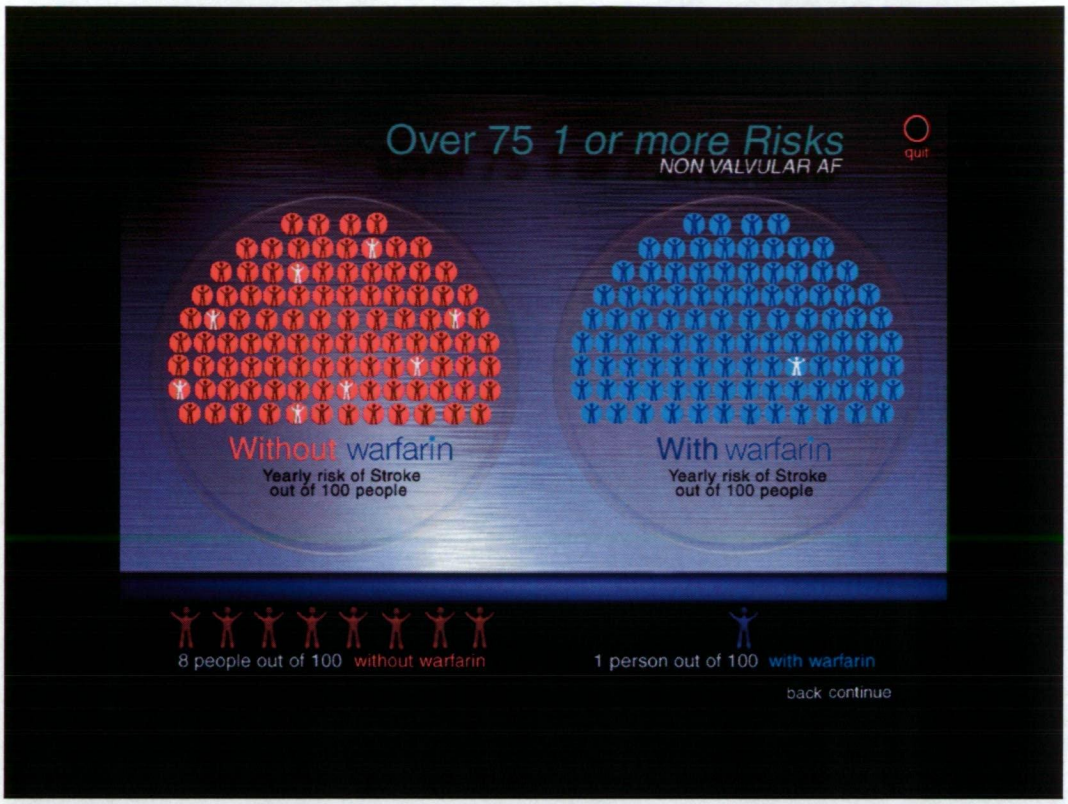
# Appendix 6

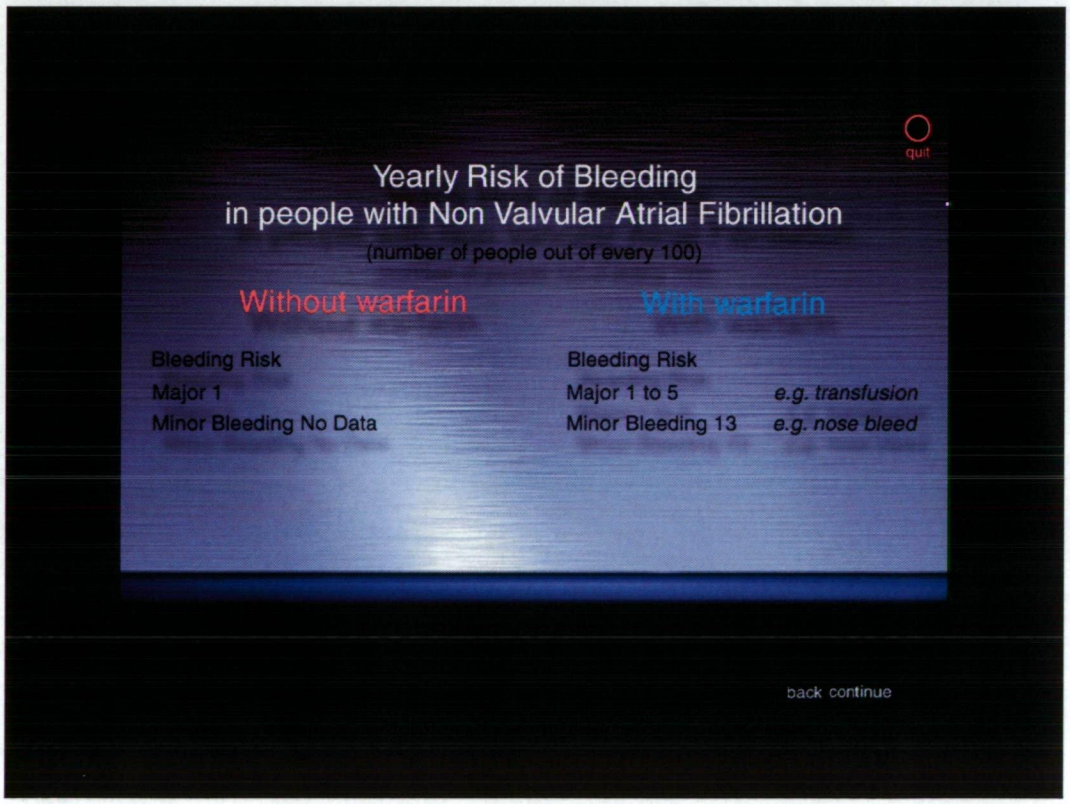
## Medical Director computer-based risk stratification

## Improving antithrombotic prescribing in AF


quit
age under 65
age 65 to 75
age 75 and over
continue


quit
age 75 and over
Non Valvular AF
Risk Factors
Hypertension
Congestive Cardiac Failure
Diabetes
Age
Prior Thromboembolism
No other Risk
1 or More Risks
Prior TIA/Stoke
back


Over 75 1 or more Risks
NON VALVULAR AF
quit
Without warfarin
Yearly risk of Stroke
out of 100 people
With warfarin
Yearly risk of Stroke
out of 100 people
8 people out of 100 without warfarin
1 person out of 100 with warfarin
back continue


quit
Yearly Risk of Bleeding
in people with Non Valvular Atrial Fibrillation
(number of people out of every 100)
Without warfarin
With warfarin
Bleeding Risk
Major 1
Minor Bleeding No Data
Bleeding Risk
Major 1 to 5
e.g. transfusion
Minor Bleeding 13
e.g. nose bleed
back continue

## Doctor/Patient Consultation Record

quit

People who have non-valvular atrial fibrillation are at risk of having a stroke. This risk also increases with age.

If people have other medical conditions the risk of stroke is increased further.

*(see Your Additional Risk Factors below).*

In many of these people treatment with warfarin can significantly reduce the risk of having a stroke.

As with most medicines treatment with warfarin has side effects. The most common side effect of warfarin is bleeding (haemorrhage), which can be major or minor.

### Yearly Risk of **STROKE** in people with Non-Valvular Atrial Fibrillation
(number of people out of every 100).

| AGE | NUMBER OF ADDITIONAL RISK FACTORS | NOT TREATED with WARFARIN | TREATED with WARFARIN |
|---|---|---|---|
| UNDER 65 | | | |
| 65-75 | | | |
| OVER 75 | 1 | 8 | 1 |

### Yearly Risk of **BLEEDING** in people with Non-Valvular Atrial Fibrillation
(number of people out of every 100).

| | **NOT TREATED** with WARFARIN | **TREATED** with WARFARIN | |
|---|---|---|---|
| Major Bleeding | 1 | 1-5 | eg Transfusion |
| Minor Bleeding | No Data | 13 | eg Nose Bleed |

### PRECAUTIONS WHEN TAKING WARFARIN

Always follow your doctor's instructions and advice when you are being treated with warfarin and tell your doctor if you experience any side effects or have other concerns.

- Avoid bleeding gums by brushing your teeth gently
- Avoid alcohol
- Wherever possible avoid activities which could result in injury or bleeding
- Carry identification stating that you are taking warfarin
- Tell your doctor if you have excessive bruising, nose bleeds, severe headaches, blood in urine or faeces, coughing up blood or any other symptoms you are concerned about.

continue

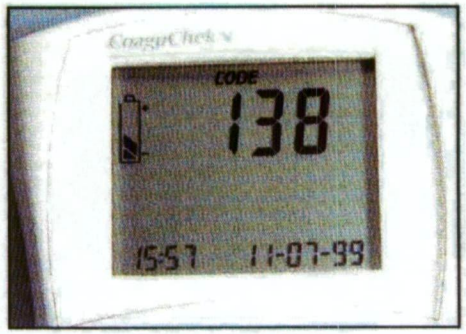
# Appendix 7

## Colour information sheet demonstrating the use of the CoaguChek S INR monitor

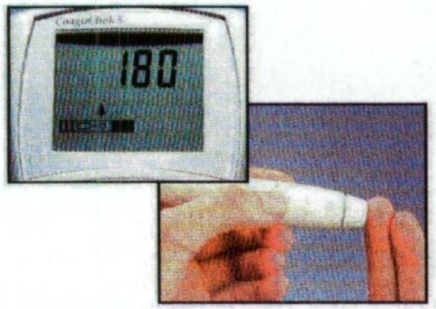
## INR monitoring projects

# *Determining the INR/Quick value using capillary blood*

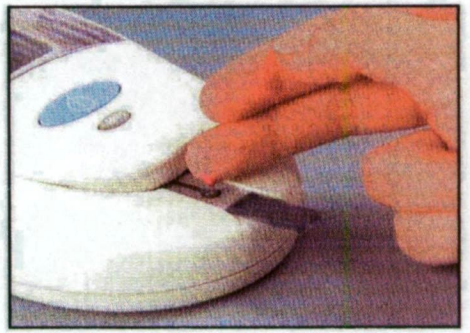
**Getting ready:** Take one test strip foil pouch out of the refrigerator and wait for at least 5 minutes to allow the test strip to come up to room temperature. The code chip from the test strip pack being used must be in the monitor. As you open each new test strip pack, place the code chip in the monitor before switching it on. Do not remove the code chip from the monitor until you start using a new pack of test strips (with a new code chip), switching the monitor off before you do so.



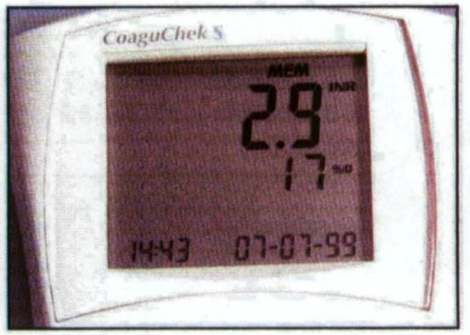

**1. Switch on the monitor and check:**
Check that the code numbers in the display match the last three digits on the test strip foil pouch and that the date and time are set correctly.



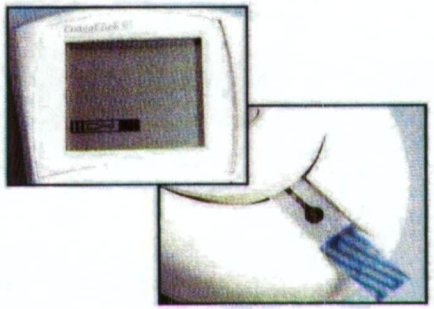

**3a. Prick your fingertip:**
A flashing drop of blood appears on the display with the number 180. The monitor is now ready and begins counting down from 180 seconds. The sample must be applied to the test strip within this time.
Now prick the tip of your middle or ring finger at the side, using the lancet device.



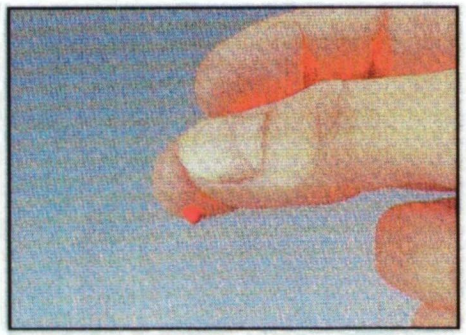
**4. Apply sample:**
Apply the first drop of blood to the flashing yellow area of the test strip within 15 seconds of pricking your fingertip. **The test area must be completely covered with blood.**




**5. Measurement:**
The CoaguChek S starts measurement as soon as the drop of blood is applied. The clock icon appears on the display and the minute hand moves until the measurement has been completed. The result is displayed after about 1 minute and is automatically stored in the monitor. Record the result in your log book.



**2. Insert the test strip:**
When the test strip icon flashes on the display, open the test strip foil pouch and insert the test strip into the monitor. The clock icon flashes next to the test strip for 45 seconds while the monitor warms up.



**3b.** Rub the outside of the finger you have pricked until a large, hanging drop of blood has formed (**Do not pinch or squeeze!**).

Please note:
The CoaguChek must be used on a stable, flat surface.

It is essential that a reasonably large drop of blood is used - it must fully cover the flashing area.

The CoaguChek is most accurate within the INR range of 2.0-3.0, and it may be appropriate to redo tests outside of this range.

For any queries, please phone Shane Jackson on 03-62262203 or 0408485430.

**The most important icons are explained on the reverse of this quick reference guide. An explanation of all symbols that can appear on the display is given in the CoaguChek S user's manual.**

# Explanation of the most important symbols

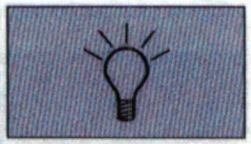

Indicates error conditions such as a test error or temperature error.


Indicates the code number of the current Code Chip.

Indicates the state of the battery power:

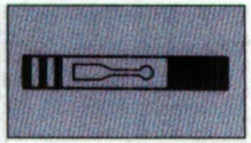
- Full power has all segments lit.
- Depleted power shows only the case lit.
- Segments disappear as power is drained.

Indicates the room temperature is out of the monitor operating range.



Indicates the room light is too bright.

Indicates the strip guide requires cleaning.



Indicates there is a strip in place, strip requested (when flashing), or test error.

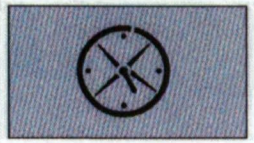
Indicates the user needs to apply a sample.

Indicates a sample application error.


Indicates the sample applied was a control solution.


Indicates the monitor is in memory retrieval mode.


Indicates the monitor is in setup mode.

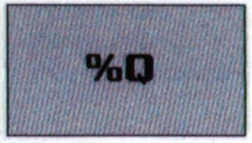


Indicates the user needs to wait for the monitor to complete an action.

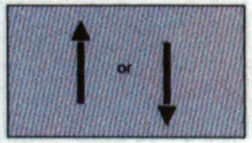
Indicates a "return for service" error. Call Roche Diagnostics.

Indicates the beeper option. When the beeper is off, the symbol flashes. When the beeper is on, the symbol does not flash.

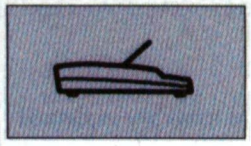

Indicates the results are displayed in INR units.




Indicates the results are displayed as Percent Quick.




Indicates the results are out of range on the primary scale.
Up Arrow - above range
Down Arrow - below range



Lid to monitor is open.

# Appendix 8

## Patient information and consent form

## Rural general practice INR monitoring

UNIVERSITY OF TASMANIA

*Tasmanian School of Pharmacy*

*Telephone: 6226 2203*

# *Testing the accuracy of a portable INR monitor compared with conventional pathology testing*

## *Information sheet*

The aim of the study is to look at the accuracy of a portable INR monitor as compared to conventional pathology testing. A portable INR monitor is a machine that can give you an INR result from a fingerprick sample of blood. This will include normal venous sampling for conventional pathology testing.

As a patient receiving care through your normal general practitioner you will undergo venous sampling for the conventional pathology testing and will be asked to give a fingerprick sample to test the accuracy of the portable INR monitor compared to pathology testing.

It is intended that the results from this study will be useful in improving the management of patients in the future on anticoagulant therapy.

Further information can be obtained from:

Professor Greg Peterson at the University of Tasmania (phone 62262197)

Shane Jackson 0408485430 or Luke Bereznicki 0438 232864

The project has received ethical approval from the Royal Hobart Hospital Ethics Committee.

If you have any concerns of an ethical nature or complaints about the manner in which the project is conducted you can contact the Chair or Secretary of the Ethics Committee.

| | | |
|---|---|---|
| Chair: | Dr Janet Vial | 62 224842 |
| Secretary: | Ms Chris Hooper | 62 262763 |

## UNIVERSITY OF TASMANIA

# *Testing the accuracy of a portable INR monitor compared with conventional pathology testing*

### *Consent Form*

1 I have read and understood the 'Information Sheet' for this study.

2 The nature and possible effects of the study have been explained to me.

3 I understand that the study involves the following procedures:

A fingerprick sample of blood for testing via the portable INR monitor will be obtained in addition to the normal venous sample for conventional pathology testing.

4 I have been informed that the results of the study may not be of any direct benefit to my medical management.

5 Any questions that I have asked have been answered to my satisfaction.

6 I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.

7 I agree to participate in this investigation and understand that I may withdraw at any time without affecting my medical care or relationship with the hospital, doctors, nursing staff and research investigators.

Name of **subject** ..... Signature .....

Date .....

Name of **witness** ..... Signature .....

Date .....

Statement by the **researcher**
I have explained this study and the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation.

Name of **researcher** ..... Signature .....

Date .....

# Appendix 9

## General practice INR monitoring data sheet

## Rural general practice INR monitoring

**Patient Questionnaire**

***Please complete this section of the questionnaire during your first consultation with the patient.***

Patient Name (to be deleted upon completion of trial):

.....

Sex: Male / Female

Age:

Reason for commencement of Warfarin therapy:

- Deep Venous Thrombosis
- Atrial Fibrillation
- Heart valve Replacement
- Other (please specify)

.....
.....

Length of time undergoing warfarin therapy:

1. Has this patient suffered any thromboembolic complications while taking warfarin?

Yes / No

If yes, please explain

.....
.....
.....
.....

2. Has this patient suffered any bleeding complications while on warfarin?

Yes / No

If yes, please explain

.....
.....
.....
.....

3. How many times a month is pathological INR testing normally performed on this patient?

.... Times per month

***Please complete the remaining questions upon completion of the trial period.***

4. Given access to the CoaguChek monitor, how many times a month would you test this patient's INR?

.... Times per month

5. Has the use of the CoaguChek monitor been more time consuming than pathological testing...

...for you? Yes / No
...for this patient? Yes / No

If yes, please explain

.....
.....
.....
.....

6. Do you feel that the use of the CoaguChek monitor has increased compliance in this patient?

Yes / No / Unsure

7. Do you feel that the use of the CoaguChek monitor has resulted in better care of this patient?

Yes / No / Unsure

8. Did this patient prefer to use the CoaguChek monitor compared to pathological testing?

Yes / No/Unsure

If yes, please explain

.....
.....
.....
.....

9. Please attach a record of recent past pathological testing for this patient if one is available [optional].

10. Would this patient be a candidate for self-management of oral anti-coagulation?

Yes /No/Unsure

## Table of Patient CoaguChek and Pathology INR Results

**Patients name (to be removed at end of study).....**
Target INR range for this patient: .....

| Date | CoaguChek INR | Pathology INR | Action Taken |
|---|---|---|---|
| | | | |
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Do you have any further comments pertaining to the CoaguChek monitor or the anticoagulant therapy of this patient?

.....
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.....
.....
.....
.....

# Appendix 10

## Doctor information form

## Rural community pharmacy-based

## INR monitoring

UNIVERSITY OF TASMANIA

*Tasmanian School of Pharmacy*

*Telephone: 6226 2203*

# Improving the outcomes of anticoagulation in rural Australia: an evaluation of pharmacist-assisted monitoring of warfarin therapy

## *Information sheet*

Dear Doctor

This pharmacy in conjunction with the University of Tasmania has agreed to partcipate in a trial of pharmacist-assisted monitoring of warfarin therapy. The aim of this study is to improve the outcomes of warfarin therapy in rural Australia. This includes an examination of the effect of free INR monitoring by the pharmacist. You as the general practitioner will be contacted regarding all INR measurements.

The pharmacist can discuss issues relating to warfarin therapy with the patient as well as performing a blood INR using a finger-prick blood sample with a portable INR monitor (a machine that can rapidly gives you an INR result from a fingerprick sample of blood, rather than the normal blood sampling for conventional pathology testing. It is similar to the blood sugar monitors used by diabetic patients). Any dose changes of warfarin will be made in consultation with you if needed

Also, we will gather some brief information from the patients (e.g. age, reason for warfarin therapy). We will also ask you for your opinion on the use of the INR monitor. This information will be kept *strictly confidential*, and only the researchers will have access to identifying data. It is intended that the results from this study will be useful in improving the management of patients placed on warfarin in rural settings.

Thank you for your assistance.

Further information can be obtained from Shane Jackson (0408485430) or Professor Greg Peterson at the University of Tasmania (phone 03-62262197).

The project has received ethical approval from the Southern Tasmania Health and Medical Human Research Ethics Committee.

If you have any concerns of an ethical nature or complaints about the manner in which the project is conducted you can contact the Chair or Executive Officer of the Ethics Committee.

| | | |
|---|---|---|
| Chair: | Dr Helen McArdle | 6222 8195 |
| Executive Officer: | Mrs Amanda McAully | 6226 2763 |

# Appendix 11

## Patient information and consent form

## Rural community pharmacy-based INR monitoring

UNIVERSITY OF TASMANIA
*Tasmanian School of Pharmacy*
*Telephone: 6226 2203*

# Improving the outcomes of anticoagulation in rural Australia: an evaluation of pharmacist-assisted monitoring of warfarin therapy

## *Information sheet*

This pharmacy in conjunction with the University of Tasmania has agreed to participate in a trial of pharmacist-assisted monitoring of warfarin therapy. The aim of this study is to improve the outcomes of warfarin therapy in rural Australia. This includes an examination of the effect of free INR monitoring by the pharmacist. The General practitioner will be contacted regarding all INR measurements.

The pharmacist can discuss issues relating to warfarin therapy with the patient as well as performing a blood INR using a finger-prick blood sample with a portable INR monitor (a machine that can rapidly give you an INR result from a fingerprick sample of blood, rather than the normal blood sampling for conventional pathology testing. It is similar to the blood sugar monitors used by diabetic patients). The General Practitioner will determine any dose changes of warfarin if needed

Also, we will gather some brief information from the patients (e.g. age, reason for warfarin therapy). We will also ask you for your opinion on the use of the INR monitor. This information will be kept *strictly confidential*, and only the researchers will have access to identifying data. It is intended that the results from this study will be useful in improving the management of patients placed on warfarin in rural settings.

Thank you for your assistance.

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| | | |
|---|---|---|
| Chair: | Dr Helen McArdle | 6222 8195 |
| Executive Officer: | Mrs Amanda McAully | 6226 2763 |

UNIVERSITY OF TASMANIA

# Improving the outcomes of anticoagulation in rural Australia: an evaluation of pharmacist-assisted monitoring of warfarin therapy

*Consent Form*

1 I have read and understood the 'Information Sheet' for this study.

2 The nature and possible effects of the study have been explained to me.

3 I understand that the study involves the following procedures:

A fingerprick sample of blood for testing via the portable INR monitor will be obtained and the result forwarded to my doctor. All patients will receive their routine medical care.

4 I have been informed that the results of the study may not be of any direct benefit to my medical management.

5 Any questions that I have asked have been answered to my satisfaction.

6 I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.

7 I agree to participate in this investigation and understand that I may withdraw at any time without affecting my medical care or relationship with the pharmacist, doctor, and research investigators.

Name of subject ---------- Signature ----------

Date ----------

Name of witness ---------- Signature ----------

Date ----------

Statement by the researcher
I have explained this study and the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation.

Name of researcher ---------- Signature ----------

Date ----------

# Appendix 12

## Data collection form

## Rural community pharmacy-based

## INR monitoring

Rural pharmacy INR monitoring patient
DATA SHEET

UNIVERSITY OF TASMANIA

| | | | |
|---|---|---|---|
| Name: | | Phone (home): | |
| Address: | | Mobile: | |
| Date of birth: | | | |

| | |
|---|---|
| Indication for anticoagulation: | |
| Target INR: | |
| Length of therapy: | |
| Doctor: | |

Other medical conditions:

Medication list:

Other relevant issues:

INR data table:

| Date | INR | Dose | Time involved | Comparison or additional | Outcome same, < / > | Pathology INR if known |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
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# Appendix 13

## Facsimile transmission form for pharmacy to general practitioner

## Rural community pharmacy-based INR monitoring

**Facsimile transmission**


UNIVERSITY OF TASMANIA

Tasmanian School of Pharmacy

**To:** Dr

**Fax number:**

**Total pages:**

**From:** Community Pharmacist

**Date:**

**Subject:** **RURAL PHARMACY INR MONITORING FAX SHEET FOR GENERAL PRACTITIONERS**

---

| | | | |
|---|---|---|---|
| Name: | | Phone (home): | |
| Address: | | Mobile: | |
| | | | |
| | | | |
| Date of birth: | | | |

| | | | | |
|---|---|---|---|---|
| Date of test: | | Comparison pathology test | Yes | No |
| Time of test: | | | | |
| INR: | | If out of target range call GP | Yes | No |

Current dose:

| Dose | Mon | Tue | Wed | Thur | Fri | Sat | Sun |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

Comments from pharmacist:

| |
|---|
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| |
| |

GPO Box 252-26 Hobart
Tasmania 7001 Australia
Telephone 03 6226 2190
Facsimilie 03 6226 2870

# Appendix 14

## Patient satisfaction survey

## Rural community pharmacy-based

## INR monitoring

# PATIENT SATISFACTION QUESTIONNAIRE

UNIVERSITY OF TASMANIA
*Tasmanian School of Pharmacy*
*Telephone: 6226 2203*

Please help us evaluate and improve the rural pharmacy anticoagulation monitoring service by answering some questions about the services you have received from the pharmacist. We are interested in your honest opinions, whether they are positive or negative. *Please answer all of the questions.* Thank you very much, we really appreciate

---

**Please Tick your Answers**

1 How satisfied are you with the warfarin monitoring conducted by your pharmacist

- ❑ Quite dissatisfied
- ❑ Indifferent or mildly dissatisfied
- ❑ Mostly satisfied
- ❑ Very satisfied

2 Has the monitoring provided by the pharmacist helped you to deal more effectively with your medication *warfarin*

- ❑ Yes, they helped a great deal
- ❑ Yes, they helped somewhat
- ❑ No, they really didn't help
- ❑ No, they seemed to make things worse

3 Which type of testing would you prefer

- ❑ Fingerprick testing at the pharmacy
- ❑ Fingerprick testing at the General Practitioners surgery
- ❑ Conventional pathology testing
- ❑ Unsure

4 Is there other information you need, or would like, about *warfarin* but have not received?

- ❑ Yes, there definitely is
- ❑ Yes, I think there is
- ❑ No, I don't think there is
- ❑ No, there definitely is not

5 Overall, how would you rate the quality of the service that you received from the pharmacist?

- ❑ Excellent
- ❑ Good
- ❑ Fair
- ❑ Poor

6 Did you find the regular *warfarin* (INR) monitoring: *(you may tick more than one)*

- ❑ painful
- ❑ informative
- ❑ motivating
- ❑ a waste of time
- ❑ interesting
- ❑ annoying
- ❑ convenient
- ❑ beneficial

7 Do you think this service would be best provided in your home or at your local pharmacy?

- ❑ Home
- ❑ Local Pharmacy
- ❑ General Practitioners Surgery (GP)

8 Do you think this service should be available to all patients on *warfarin* therapy?

- ❑ Yes
- ❑ No

9 If this was a regular service, would you be prepared to pay it?

- ❑ Yes
- ❑ No

10 If you answered yes to the previous question, how much would you be prepared to pay per visit?

- ❑ $1 - $5
- ❑ $6 - $10
- ❑ $11 - $15
- ❑ $16 +

11 If you wish to make any other comments, please feel free to do so in the space provided. If more space is required, use the back of this sheet.

_____

_____

_____

_____

_____

_____

***Thank you for taking the time to fill out this questionnaire***
***Please post in the reply-paid envelope supplied***

# Appendix 15

## Patient information and consent form

## Improving warfarin initiation

UNIVERSITY OF TASMANIA
*Tasmanian School of Pharmacy*
*Telephone: 6226 2203*

# Royal Hobart Hospital and University of Tasmania

***Home follow-up of patients commenced on warfarin therapy***

# *Information sheet*

The aim of this study is to improve the outcomes of warfarin therapy. This includes an examination of the effect of regular, free follow-up sessions with a pharmacist visiting you at home, with regular blood INR monitoring. An INR measurement is a measure of how thick or thin your blood is, and is used to adjust your warfarin dose. The pharmacist, in consultation with your doctor, can also assist with any medication problems or queries.

Consecutive patients commenced on warfarin in hospital are being randomly allocated to either an 'intervention' or 'control group'. There is a 50:50 chance of being allocated to each group. Patients in the 'intervention' group will receive a pharmacist visit at home on alternate days on four occasions, with an initial visit two days after discharge from hospital (the pharmacist will visit you four times in eight days). At each session, the pharmacist can discuss issues relating to warfarin therapy, as well as performing a blood INR using a finger-prick blood sample with a portable INR monitor (a machine that can rapidly give you an INR result from a fingerprick sample of blood, rather than the normal blood sampling for conventional pathology testing. It is similar to the blood sugar monitors used by diabetic patients). There will be a final visit at 3 months after discharge from hospital.

Patients in the 'control group' will be visited at 8 days after discharge from hospital and you will need to receive normal care from your general practitioner, the pharmacist will only take a blood sample for data collection. The pharmacist will then visit you again 3 months after discharge from hospital.

All the INR results will be forwarded to your regular doctor.

Also, we will take information (age, relevant medical and surgical history) from your hospital medical records. This information will be kept *strictly confidential*, and only the researchers will have access to identifying data.

It is intended that the results from this study will be useful in improving the management of patients placed on warfarin.

Further information can be obtained from Greg Peterson at the University of Tasmania (phone 62262197).

The project has received ethical approval from the Southern Tasmania Health and Medical Human Research Ethics comittee.

If you have any concerns of an ethical nature or complaints about the manner in which the project is conducted you can contact the Chair or Secretary of the Ethics Committee.

| | | |
|---|---|---|
| Chair: | Dr Helen McArdle | |
| Executive Officer : | Ms Amanda McAully | 62 262763 |

# Royal Hobart Hospital and University of Tasmania

## *Home follow-up of patients commenced on warfarin therapy*

Consent Form

1. I have read and understood the 'Information Sheet' for this study.
2. The nature and possible effects of the study have been explained to me.
3. I understand that the study involves the following procedures:

   Consecutive patients commenced on warfarin in hospital are being randomly allocated to either an 'intervention' or 'control group'. There is a 50:50 chance of being allocated to each group. Patients in the 'intervention' group will receive a pharmacist visit at home on alternate days on four occasions, with an initial visit two days after discharge from hospital. At each session, the pharmacist will discuss issues relating to warfarin therapy, as well as performing a blood INR using a finger-prick blood sample. The pharmacist will also attempt to help with any medication problems or queries. There will be a final visit at 3 months after discharge from hospital. Patients in the 'control group' will only be visited at 3 months after discharge from hospital. All patients will receive their routine medical and nursing care. All the INR results will be forwarded to your regular doctor.
4. I have been informed that the results of the study may not be of any direct benefit to my medical management.
5. Any questions that I have asked have been answered to my satisfaction.
6. I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.
7. I agree to participate in this investigation and understand that I may withdraw at any time without affecting my medical care or relationship with the hospital, doctors, nursing staff and research investigators.

Name of **subject** ..... Signature .....

Date .....

Name of **witness** ..... Signature .....

Address .....

Date .....

Statement by the **researcher**

I have explained this study and the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation.

Name of **researcher** .....

Signature of **researcher** ..... Date .....

# Appendix 16

## Patient education document

## Improving warfarin initiation

# One page guide to warfarin treatment*

1. Warfarin belongs to a class of medications called anticoagulants ("blood thinners")

   Warfarin keeps blood clots from forming or getting larger.

2. Many medications can change the way warfarin works. Ask your doctor or pharmacist about using any other medication, including over-the counter medications, vitamins and herbal products

3. Make sure your doctor or pharmacist know if you are taking aspirin or aspirin-like medications, such as medications for pain relief and the common cold

4. Avoid drinking large amounts of alcohol

5. Certain foods will change the way warfarin works. Do not change your diet while taking warfarin. Foods that contain vitamin K (such as lettuce, spinach, broccoli, cabbage, cauliflower or liver) decrease the anti-clotting effect of warfarin. If you eat foods that have vitamin K, **do not** change the amount of these foods that you normally eat per week. The main point regarding diet is to eat a consistent amount of foods per week that contain vitamin K.

6. It is very important to have regular blood tests while taking warfarin. The test is called an INR, and it measures how thin your blood is compared to normal.

7. You should carry an identification card that shows you are taking warfarin.

8. Make sure your doctor or dentist knows you are taking warfarin before you have any surgery or dental work.

9. You should report the following to your doctor immediately

   Bleeding from the gums or nose

   Coughing up blood

   Red or black bowel motions

   Red or dark-brown coloured urine

   Unusually heavy menstrual bleeding

   Heavy bleeding from cuts or wounds that does not stop

   Easy bruising

   Severe headache

10. **If you miss a dose:** Take the missed dose as soon as possible. If you do not remember until the next day, skip the missed dose. Only take your usual dose for the day. You should not use two doses at the same time.

*Adapted from the institute for clinical systems improvement (www.icsi.org)

# Appendix 17

## Initial correspondence with the general practitioner (Home Monitoring group)

## Improving warfarin initiation

UNIVERSITY OF TASMANIA

*Tasmanian Schools of Pharmacy & Medicine*

*Telephone: 6226 2203*

Dear Dr

**HOME FOLLOW-UP OF PATIENTS COMMENCED ON WARFARIN THERAPY**

Your patient .....has been recruited into a study of patients recently discharged from the Royal Hobart Hospital. This study aims to improve the outcomes of initiation of warfarin therapy.

The study has been approved by the Royal Hobart Hospital Research and Ethics Committees. All patients have given their informed consent to participate. I have attached for you a copy of the information sheet that the patient has received.

Your patient has been randomised to the **intervention** group. Patients in the 'intervention' group will receive a pharmacist visit at home on alternate days on four occasions, with an initial visit two days after discharge from hospital. At each session, the pharmacist will discuss issues relating to warfarin therapy, as well as performing a blood INR using a finger-prick blood sample with a portable INR monitor (a machine that can rapidly give you an INR result from a fingerprick sample of blood, rather than the normal blood sampling for conventional pathology testing. It is similar to the blood sugar monitors used by diabetic patients). There will be a final visit at 3 months after discharge from hospital. You will be contacted regarding all INRs and suggestions related to warfarin therapy

If you have any queries or require further information, please do not hesitate to call me on 0408485430

Yours sincerely,

Shane Jackson B.Pharm Hons
Project Supervisor

# Appendix 18

## General practitioner information sheet

## Improving warfarin initiation

UNIVERSITY OF TASMANIA

*Tasmanian Schools of Pharmacy & Medicine*

*Telephone: 6226 2203*

## Royal Hobart Hospital and University of Tasmania

***Home follow-up of patients commenced on warfarin therapy***

# *Information sheet*

Dear Doctor

Your patient has been enrolled in a study to evaluate the use of home follow-up of patients commenced on warfarin therapy. The aim of this study is to improve the outcomes of warfarin therapy. This includes an examination of the effect of regular, free follow-up sessions with a pharmacist visiting patients at home, with blood INR monitoring. The pharmacist, in consultation with the patient's doctors, will also assist with any medication problems or queries.

Consecutive patients commenced on warfarin in hospital are being randomly allocated to either an 'intervention' or 'control group'. There is a 50:50 chance of being allocated to each group. Patients in the 'intervention' group will receive a pharmacist visit at home on alternate days on four occasions, with an initial visit two days after discharge from hospital. At each session, the pharmacist will discuss issues relating to warfarin therapy, as well as performing a blood INR using a finger-prick blood sample with a portable INR monitor (a machine that can rapidly give you an INR result from a fingerprick sample of blood, rather than the normal blood sampling for conventional pathology testing. It is similar to the blood sugar monitors used by diabetic patients). There will be a final visit at 3 months after discharge from hospital.

Patients in the 'control group' will be visited at Day 8 and also at 3 months after discharge from hospital. All patients will receive their routine medical and nursing care.

Further information can be obtained from Greg Peterson at the University of Tasmania (phone 62262197).

The project has received ethical approval from the Royal Hobart Hospital Ethics Committee.
If you have any concerns of an ethical nature or complaints about the manner in which the project is conducted you can contact the Chair or Secretary of the Ethics Committee.

| | | |
|---|---|---|
| Chair: | Dr Janet Vial | 62 224842 |
| Secretary: | Ms Amanda McAully | 62 262763 |

# Appendix 19

## Final correspondence with the general practitioner

## Improving warfarin initiation

UNIVERSITY OF TASMANIA

*Tasmanian School of Pharmacy*

*Telephone: 6226 2203*

**Home Follow-up of patients commenced on warfarin therapy**

**EVALUATION BY GENERAL PRACTITIONERS**

Dear Dr,

I am writing to request your feedback regarding the above study.

The aim of this study was to optimise the benefit that patients receive from taking the anticoagulant warfarin, through regular home visits and INR monitoring, dietary information and education.

Your patient ..... has been participating in this study, and we would be interested in hearing your comments and feedback. The patients INR results for the duration of the study are displayed. Enclosed please find a questionnaire for you to complete, and return in the reply paid envelope.

| **Days post discharge** | 2 | 4 | 6 | 8 |
|---|---|---|---|---|
| **Date 2002** | 20/2 | 22/2 | 24/2 | 26/2 |
| **INR (coaguchek)** | 2.7 | 2.9 | 3.1 | 2.8 |
| **Previous Dose (mg)** | 2 | 2 | 2 | 1 |

If you require more specific information regarding your patient's participation, or a copy of the completed study, please don't hesitate to call me on 0408485430

Thank you in anticipation.

Yours sincerely,

Shane Jackson B.Pharm Hons
Project Manager

# Appendix 20

## Initial correspondence with the general practitioner (Usual Care group)

## Improving warfarin initiation

UNIVERSITY OF TASMANIA

*Tasmanian Schools of Pharmacy & Medicine*

*Telephone: 6226 2203*

Dear Dr

**HOME FOLLOW-UP OF PATIENTS COMMENCED ON WARFARIN THERAPY**

Your patient has been recruited into a study of patients recently discharged from the Royal Hobart Hospital. This study aims to improve the outcomes of initiation of warfarin therapy.

The study has been approved by the Royal Hobart Hospital Research and Ethics Committees. All patients have given their informed consent to participate. I have attached for you a copy of the information sheet that the patient has received.

Your patient has been randomised to the **control** group. Patients in the control group will receive a pharmacist visit at home on Day 8 and at 90 days after discharge from hospital. The patient will be asked to report any adverse effects of warfarin therapy at this time.

If you have any queries or require further information, please do not hesitate to call me on 0408485430

Yours sincerely,

Shane Jackson B.Pharm Hons
Project Supervisor

# Appendix 21

## Home visit data collection form

## Improving warfarin initiation

# IMPROVING THE OUTCOMES OF ANTICOAGULATION: AN EVALUATION OF HOME FOLLOW-UP OF WARFARIN THERAPY

*(Tick where appropriate)*

## 1 PERSONAL DATA

| | | | |
|---|---|---|---|
| Study Number: | | UR Number:<br>Control<br>Intervention | |
| Admitting Unit: | GP: | | IP/OP: |
| Age: | | Sex: | |
| Smoking history:<br>Lives alone<br>Ht<br>BMI <20 20-25 | | Alcohol intake:<br>Instutionalised<br>Wt<br>>25 | |
| Diagnosis on admission: | | | |
| Admission date: (latest) | | Discharge date: | |

## 2 REASONS FOR USE:

| | |
|---|---|
| Atrial Fibrillation<br>Valve replacement<br>DVT/PE<br>Other ( please specify) | Warfarin use in the past ( yes/no) |

## 11 ANTICOAGULANT MONITORING FOR WARFARIN ( AT HOME)

| Date and INR | Dose suggested to GP | Dose given |
|---|---|---|
| Day 2<br>Day 4<br>Day 6<br>**Day 8** | | |

## 3 MEDICATIONS ON ADMISSION AND DOSE

| |
|---|
| Interacting medications (number)<br>Minimally significant<br>Moderately significant<br>Very significant |

## 4 MEDICATIONS ON DISCHARGE AND DOSE

| |
|---|
| Interacting medications (number)<br>Minimally significant<br>Moderately significant<br>Very significant |

## 5 CLINICAL DISEASE RISK FACTOR (AND DURATION/DATE)

| | TYPE: |
|---|---|
| Previous stroke | |
| Previous TIA | |
| Other embolic events<br>Family history of embolic events | |
| Hypertension<br>Average blood pressure | |
| Diabetes | |
| Angina | |
| Previous AMI | |
| CHF | |
| Mitral valve disease | |
| Thyrotoxicosis | |
| Prosthetic heart valve | |
| Peripheral arterial disease | |
| Other cardiac diseases | |
| Malignancy | |
| | |

## 8 CONTRAINDICATIONS TO ANTITHROMBOTIC (AS IN APP)

| *Warfarin* | | | |
|---|---|---|---|
| History of haemorrhagic<br>Tendency<br>Previous exposure to warfarin<br>Recent or contemplated surgery (CNS, eye)<br>Spinal puncture, diagnostic procedure | | Bleeding tendencies associated with active ulceration/overt bleeding of GIT, RT, GU, cerebral haemorrhage, aneurysms-cerebral, dissecting aorta, pericarditis, pericardial effusions, bacterial endocarditis | |
| Chronic liver disease | | Chronic alcoholism | |
| GGT | | ALA/ALP | |
| BILIRUBIN | | ALBUMIN | |
| Blood dyscrasia (thrombocytopaenia) | | Unsupervised dementia/psychosis | |
| Allergy | | Falls | |
| Malignant H/T | | | |

## 11 ANTICOAGULANT MONITORING FOR WARFARIN ( IN HOSPITAL )

| INR | Date | dose |
|---|---|---|
| | | |
| | | |
| Discharge INR | | |

## 11 ANTICOAGULANT MONITORING FOR WARFARIN ( AT HOME)

| INR | Date | dose | Compliance |
|---|---|---|---|
| | | | ( pill count) |
| | Day 2<br>Day 4<br>Day 6<br>**Day 8** | | |

DAY 2 FOLLOW UP
DETECTION OF DRUG RELATED PROBLEMS

POOR COMPLIANCE

DRUG INTERACTIONS

DRUG FOOD INTERACTION

OTHER DRUG RELATED PROBLEMS

TIME SPENT WITH PATIENT

DAY 4 FOLLOW UP
DETECTION OF DRUG RELATED PROBLEMS

POOR COMPLIANCE

DRUG INTERACTIONS

DRUG FOOD INTERACTION

OTHER DRUG RELATED PROBLEMS

LEVEL OF UNDERSTANDING OF WARFARIN /10

TIME SPENT WITH PATIENT

DAY 6 FOLLOW UP
DETECTION OF DRUG RELATED PROBLEMS

POOR COMPLIANCE

DRUG INTERACTIONS

DRUG FOOD INTERACTION

OTHER DRUG RELATED PROBLEMS

LEVEL OF UNDERSTANDING OF WARFARIN /10

TIME SPENT WITH PATIENT

DAY 8 FOLLOW UP
DETECTION OF DRUG RELATED PROBLEMS

POOR COMPLIANCE

DRUG INTERACTIONS

DRUG FOOD INTERACTION

OTHER DRUG RELATED PROBLEMS

LEVEL OF UNDERSTANDING OF WARFARIN /10

TIME SPENT WITH PATIENT

## 12 CLINICAL OUTCOMES ( FOR 90 DAY FOLLOW-UP)

| | |
|---|---|
| Bleeding complications<br>Date of initiation of antithrombotics<br>Dose of antithrombotic<br>Interval between complications and prophylaxis initiation | |
| Type | |
| Date | |
| Morbidity<br>Intracranial haemorrhage<br>CT scanning<br>Bleeding peptic ulcer<br>Blood transfusion required | |
| Stroke/TIA<br>Date<br>Interval between AF diagnosis and stroke | |
| Type | |
| Date | |
| Prognosis<br>On warfarin at 90 days | |

## 11 ANTICOAGULANT MONITORING FOR WARFARIN ( BETWEEN DAY 8 AND 90)

| INR | Date | dose |
|---|---|---|
| | | |
| | | |

14 5-point scoring system

| | |
|---|---|
| Age >65 | Low |
| History of GI bleeds | Medium |
| History of stroke | high |
| Comorbid conditions<br>AMI DM | Cr (>1.5mg/dL) CRCL<br>Hct (0.30) |

Compliance at 90 days

# Appendix 22

## Patient satisfaction survey

## Improving warfarin initiation

# PATIENT SATISFACTION QUESTIONNAIRE

UNIVERSITY OF TASMANIA

*Tasmanian School of Pharmacy*

*Telephone: 6226 7526*

Please help us evaluate and improve the pharmacy service by answering some questions about the services you have received from the pharmacist, *Shane Jackson*. We are interested in your honest opinions, whether they are positive or negative. *Please answer all of the questions.* Thank you very much, we really appreciate your help.

---

**Please Tick your Answers**

1 How satisfied are you with the amount of contact you had with the pharmacist?

- ❑ Quite dissatisfied
- ❑ Indifferent or mildly dissatisfied
- ❑ Mostly satisfied
- ❑ Very satisfied

2 Has the information and other services provided by the pharmacist helped you to deal more effectively with your new medication *warfarin*

- ❑ Yes, they helped a great deal
- ❑ Yes, they helped somewhat
- ❑ No, they really didn't help
- ❑ No, they seemed to make things worse

3 Did you get the kind of information and other services you wanted from the pharmacist?

- ❑ No, definitely not
- ❑ No, not really
- ❑ Yes, generally
- ❑ Yes, definitely

4 Is there other information you need, or would like, about *warfarin* but have not received?

- ❑ Yes, there definitely is
- ❑ Yes, I think there is
- ❑ No, I don't think there is
- ❑ No, there definitely is not

5 Overall, how would you rate the quality of the service that you received from the pharmacist?

- ❑ Excellent
- ❑ Good
- ❑ Fair
- ❑ Poor

6 Did you find the regular *warfarin* (INR) monitoring: *(you may tick more than one)*

- ❑ painful
- ❑ informative
- ❑ motivating
- ❑ a waste of time
- ❑ interesting
- ❑ annoying
- ❑ too frequent
- ❑ beneficial

7 Do you think this service would be best provided in your home or at your local pharmacy?

- ❑ Home
- ❑ Local Pharmacy

8 Do you think this service should be available to all patients commencing *warfarin* therapy?

- ❑ Yes
- ❑ No

9 If this was a regular service, would you be prepared to pay it?

- ❑ Yes
- ❑ No

10 If you answered yes to the previous question, how much would you be prepared to pay per visit?

- ❑ $1 - $5
- ❑ $6 - $10
- ❑ $11 - $15
- ❑ $16 +

11 If you wish to make any other comments, please feel free to do so in the space provided. If more space is required, use the back of this sheet.

_____

_____

_____

_____

_____

_____

***Thank you for taking the time to fill out this questionnaire***
***Please post in the reply-paid envelope supplied***

# Appendix 23

## Patient knowledge questionnaire

## Improving warfarin initiation

Evaluation of patients knowledge regarding anticoagulant therapy
Shane Jackson
Tasmanian School of pharmacy, University of Tasmania

**We are interested in finding out about your general health and the anticoagulant (warfarin) treatment that you are now receiving.**

1 Since starting warfarin would you say that your general health has: please **circle**)

Improved Worsened Stayed the same

2 As far as you know, **circle** which of the following are reasons for your present warfarin treatment?

(DVT) – blood clot in leg vein Heart surgery

Atrial Fibrillation Stroke

PE – blood clot in lung Heart disease

Anything else?

3 Do you worry about being on warfarin treatment? Please **circle**

A lot A little Not at all

If so, what are your concerns?

4 When you left the Royal Hobart Hospital (RHH) were you handed a "warfarin booklet"? please **circle**

Yes No Not sure

5 Were you told **how** warfarin works, and was this clear? Please **circle**

Yes, and clear Yes, but not clear No

Could you briefly explain in your own words how warfarin works

_____

_____

_____

_____

6 Were you told of the **possible problems with warfarin treatment**, and was this clear? please **circle**

Yes, and clear | Yes, but not clear | No

7 Were you told what to do if you have a **nosebleed or bruising** and was this clear? Please **circle**

Yes, and clear | Yes, but not clear | No

8 Were you told what **drugs to avoid** and was this clear? Please **circle**

Yes, and clear | Yes, but not clear | No

9 Were you given **advice on drinking alcohol** and was this clear to you? Please **circle**

Yes, and clear | Yes, but not clear | No

10 Could starting a new treatment or any other preparation affect your warfarin treatment? Please **circle**

Yes | No | Don't know

11 The following are statements about any patient drinking alcohol when receiving warfarin treatment (Please circle Yes or No for each statement)

| | | |
|---|---|---|
| Alcohol can affect anticoagulant treatment | Yes | No |
| Alcohol must be avoided totally | Yes | No |
| 8 units of alcohol a night is OK ( for example 8 glasses or beer or wine) | Yes | No |
| 1 unit of alcohol a night is OK ( for example 1 glass of beer or wine) | Yes | No |

12 Of the list below, **CIRCLE** which of the following factors could interfere with your warfarin therapy.

| | |
|---|---|
| Aspirin | Some illnesses |
| Weather conditions | Missing a dose of warfarin |
| Coffee | Nurofen |
| Herbal remedies | Antacids |
| Panadol | Some foods |

13 **CIRCLE** which of the following could be possible side effects of taking the wrong (too little or too much) amount of warfarin? Please do not be alarmed, some of the items are wrong,

| | |
|---|---|
| Blood in stools | Ringing in the ears |
| Nausea | Nose bleeds |
| Blood in the urine | Sleeplessness |
| Nervousness | Prolonged bleeding after cuts |
| Blood clots | Bruising without injury |
| High blood pressure | Loss of appetite |
| Weakness | |

14 **Before the visit** today by Shane Jackson, do you know what your most recent INR was? (please **circle**)

Yes No

What was it?

If you wish to make any other comments, please feel free to do so in the space provided. If more space is required, use the back of this sheet.

_____

_____

_____

_____

_____

_____

***Thank you for taking the time to fill out this questionnaire***
***Please post in the reply-paid envelope supplied***
***If you have any further comments feel free to use the back of the page***